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THE UNIVERSITY OF ALBERTA

STUDIES ON THE TOTAL SYNTHESIS OF SICCANIN

BY

B. RAMANI

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA
SPRING, 1987

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STUDIES ON THE TOTAL SYNTHESIS OF SICCANIN

submitted by B. RAMANI in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry.

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Date FEB 06 1987

TO

My Parents

And to

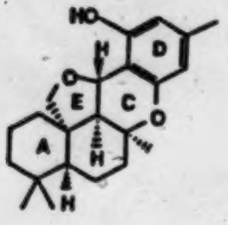
My Country

ABSTRACT

This thesis describes the results obtained from the synthetic studies on the antifungal antibiotic sesquiterpene siccanin (I) of the drimane family, cumulating in the total synthesis of the methyl ether of an unnatural stereoisomer isosiccanin (II).

The key step of the synthetic approach is the Diels-Alder addition of 2-carbomethoxy-4,4-dimethylcyclohexa-2,5-dienone and 5-benzyloxy-3-methyl-1,3-pentadiene to give adduct III, which possesses the carbon skeleton of the sesquiterpene unit of the naturally occuring compound with the correct stereochemistry. Subsequent modifications of the functionalities of III, including the removal of the enone system, the reduction of the ester to the alcohol level and the transformation of the benzyl ether moiety to an aldehyde, gave rise to unsaturated aldehyde IV. Addition of the Grignard reagent, prepared from orcinol dimethyl ether, to compound IV resulted in the formation of alcohol V. This compound was converted to isosiccanin methyl ether (VI) by two consecutive ether ring closures.

In order to apply this approach to the synthesis of the naturally occuring compound I, it is necessary to rectify the stereochemistry of the two interrelated asymmetric centres present in ring C. A brief study towards this end has been carried out and the results are also discussed.



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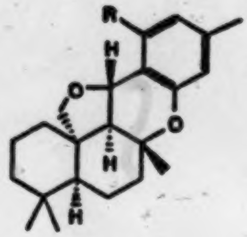
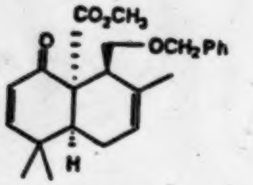


II R = OH

VI R = OCH$_3$



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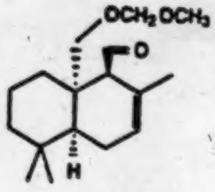

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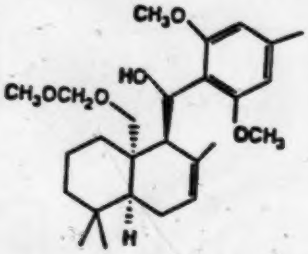

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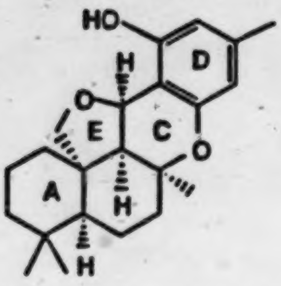
INTRODUCTION

Siccanin (**1**), a sesquiterpene of the drimane family, was isolated by Ishibashi in 1963[1] from the culture broth of *Helminthosporium siccans* Drechsler, which is a parasitic organism of rye grass, *Lothium multifolium* Lam. Structural studies of siccanin were carried out by Nozoe, Ishibashi and co-workers.[2,3] By a combination of chemical degradation and spectroscopic analysis, they proposed the gross structure as shown in formula **1** for siccanin. This assignment was unequivocally confirmed by a single crystal X-ray analysis on its *p*-bromobenzenesulfonate derivative **2**, which also resulted in the elucidation of its stereochemistry, including the absolute configuration.

Along with siccanin, siccanochromene-E (**3**) was isolated as a minor metabolite.[2] Inspection of structures **1** and **3** suggests that these compounds might be derived biogenetically by the combination of a sesquiterpene unit and an orsellinate moiety and hence can be classified as "prenyl phenols". Since siccanin is structurally related to grifolin (**4**)[5] and tauranin (**5**),[6] it was thought that these compounds might have been produced via similar biosynthetic pathways. However, the unusual *cis-syn-cis* fusion of the A,B and C ring junctions of siccanin aroused considerable interests in its biosynthetic studies, especially on the cyclisation mechanism leading to the ring junctions. Extensive studies to this end uncovered several biosynthetic intermediates related to



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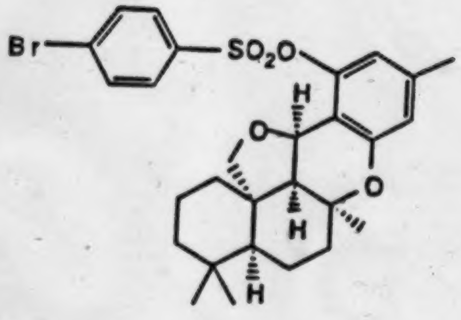

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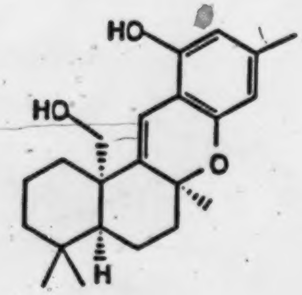

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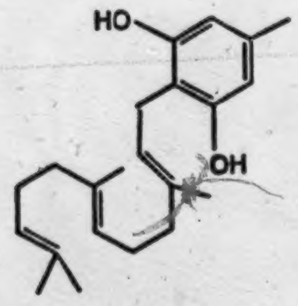

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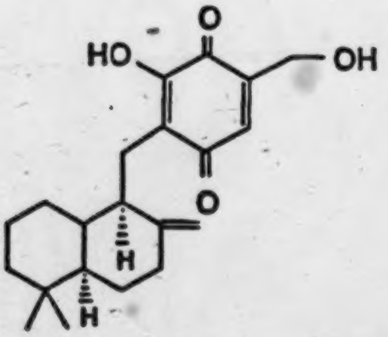

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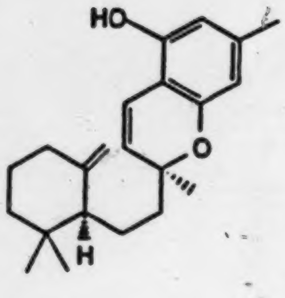
siccanin from the culture broth, which have been identified as siccanochromene-A (**6**),[7] siccanochromene-B (**7**),[7] siccanochromene-C (**8**),[7] siccanochromene-D (**9**),[8] siccanochromene-E (**3**),[2] siccanochromene-F (**10**),[8] siccanochromenic acid (**11**)[9] and pre-siccanochromenic acid (**12**).[9] Comparing the structures of these metabolites, it is possible to postulate a biosynthetic pathway leading to siccanin[10] as shown in Scheme 1. This postulation was confirmed by feeding experiments.[11-13]

It was found that the enzyme system from the disrupted cells of the fungi could convert mevalonic acid to *trans*-γ-monofarnesol derivative **14**.[11] Incubation of *trans*, *trans*-(4,8,12-^{14}C)-farnesyl pyrophosphate (**13**) in the same system along with the aromatic co-substrate orsellinic acid yielded **6**.[12] Furthermore, incubation of tritium labelled **6** resulted in tritium labelled siccanin.[13] These results lent support to the above biosynthetic proposal.

Siccanin was found to be effective against various human pathogenic fungi such as *Trichophyton*, *Epidermophyton*, and *Microsporum*.[14,15] The minimum inhibitory concentration against these organisims was found to be as low as 0.4-6.3 µg/ml even after two weeks of incubation. Other fungi such as *Aspergillus*, *Penicillium*, *Alternaria* and *Piricularia* were inhibited at a higher concentration level of 12.5 µg/ml.[9] A lesser degree of inhibition or no inhibition was noted for yeast and bacteria.[16]



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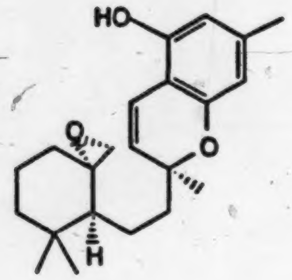

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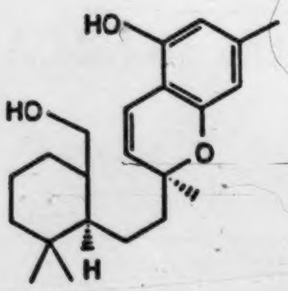

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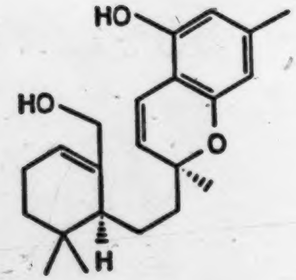

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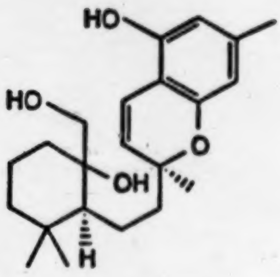

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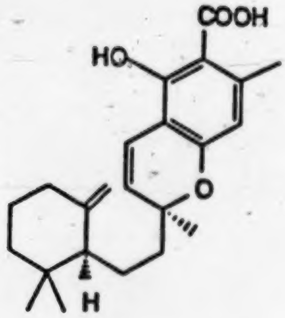

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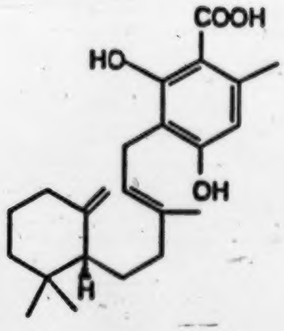

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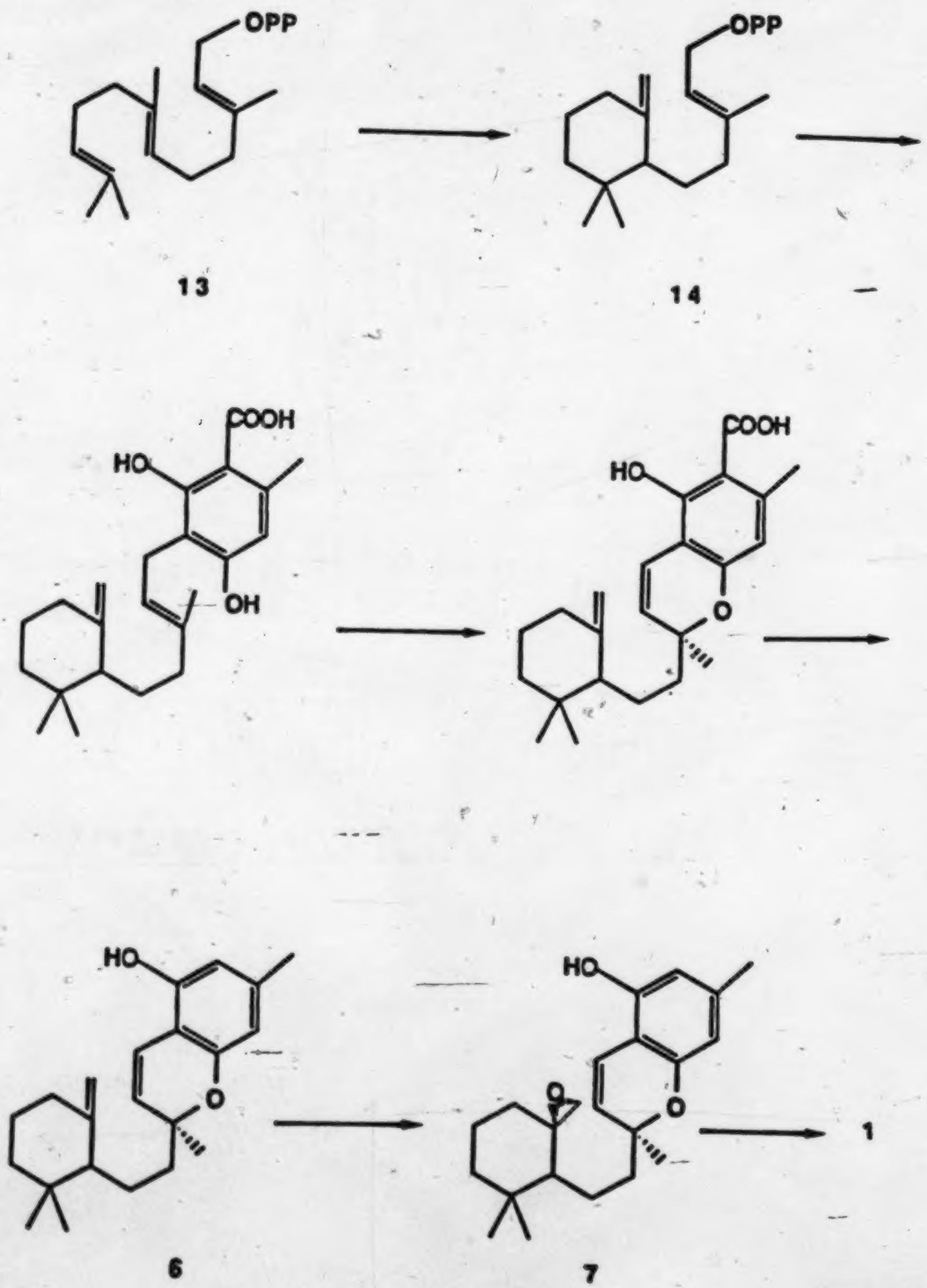


Scheme 1

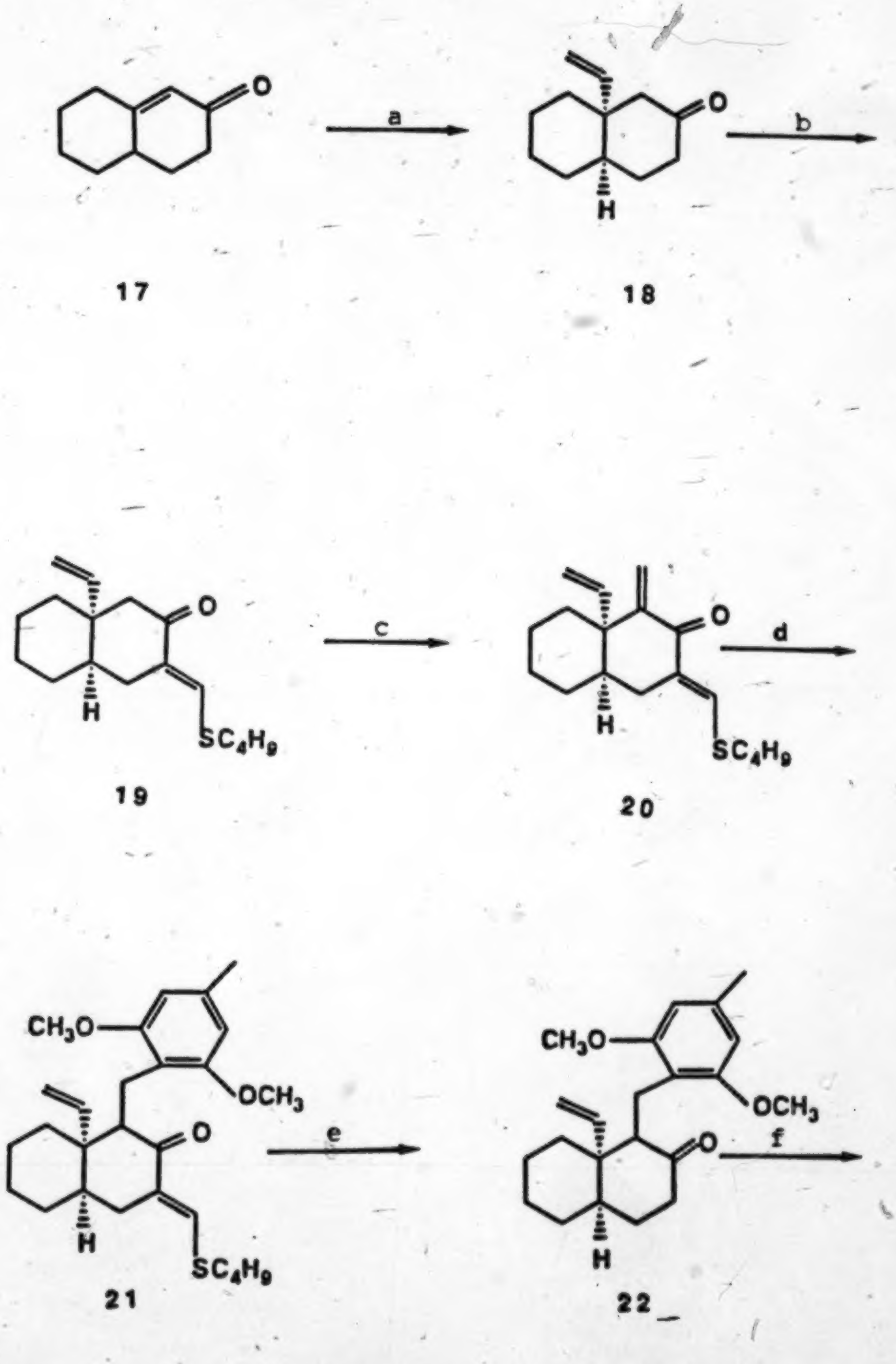
It was revealed by *in vitro* studies [15] that siccanin acts on these organisms by inhibiting their nucleic acid synthesis and respiration. However, the primary site(s) of action by siccanin remains to be determined. In spite of its high activity against various fungi mentioned above, lethal dose values (LD-50) of siccanin in male mice were found to be as high as 1.72 g/kg body weight for intraperitoneal administration.[17]

Synthetic analogues of siccanin obtained by the introduction of further substituents to the aromatic ring were found to possess lower biological activity to the extent of complete loss of activity.[16] Further work by Seki and co-workers [18] revealed that the introduction of an oxygen functional group in the C-3 position or contraction of the A ring decreases its activity, and opening of either the A or E ring makes it inactive.

Considerable efforts have been made towards the synthesis of siccanin because of its high antibiotic activity and unique *cis-syn-cis* fused drimane skeleton. Oida and co-workers [19-21] attempted the synthesis by an approach involving the initial formation of an intermediate containing the A, B and D rings of siccanin. This approach, on a model compound, is illustrated in Scheme 2.

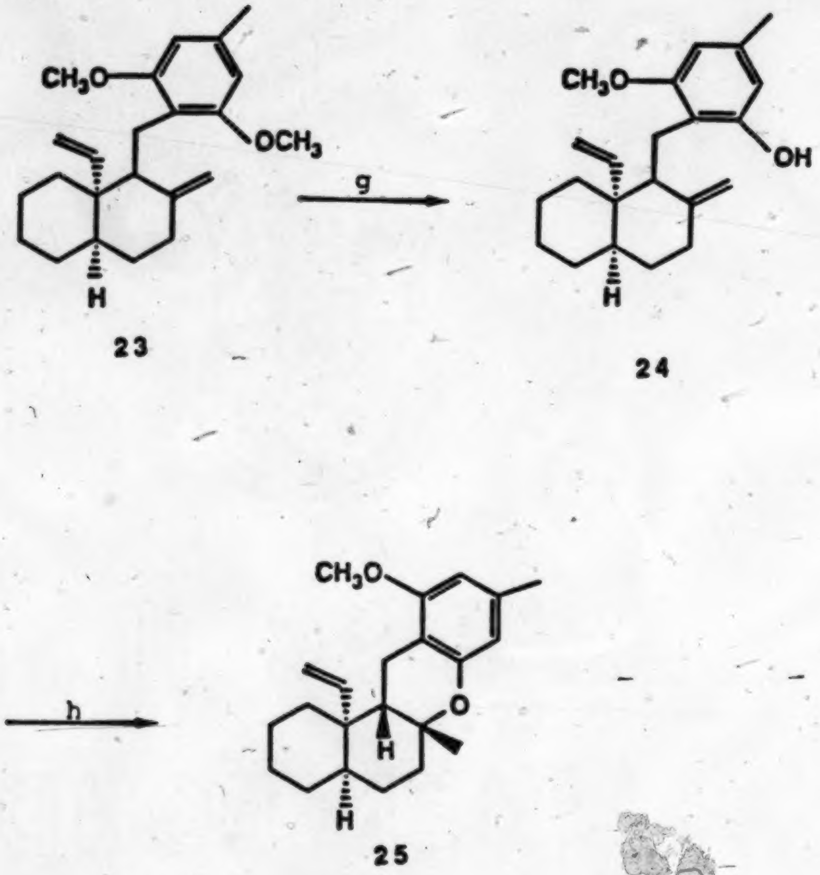
Enone **17** was subjected to 1,4-addition with vinylmagnesium chloride in the presence of cuprous ions to furnish decalone **18**. The C-3 position of **18** was blocked by acylation with ethyl formate and sodium methoxide followed by treatment with *n*-butyl mercaptan to yield dienone **19**. The enolate ion of **19**, obtained on treatment with sodium methylsulfinylmethide, was quenched with paraformaldehyde. The compound **20** thus obtained underwent clean 1,4-addition on treatment with the lithium salt of orcinol dimethyl ether to give an isomeric mixture of the ketones **21**. Heating **21** in a 25% aqueous solution of potassium hydroxide at reflux yielded a single isomer **22**. Wittig reaction of **22** with methylenetriphenylphosphorane in dimethyl sulfoxide resulted in the formation of compound **23**. Selective demethylation of **23** with sodium ethanethiolate in refluxing *N,N*-dimethylformamide gave phenol **24**, which was readily cyclised to the tetracyclic compound **25** on treatment with *p*-toluenesulfonic acid. Because only the undesired *cis-anti-cis* stereochemistry was produced, this synthetic approach to siccanin is apparently not useful without substantial modifications.

The only existing total synthesis of siccanin was reported by Yoshikosi and co-workers in 1981.[22] As shown in Scheme 3, their synthesis began with Robinson annelation of the known keto ester **26** with methyl vinyl ketone in the presence of sodium methoxide and methanol to yield octalone **27**. Deconjugative dimethylation of **27** with methyl iodide in the presence of sodium hydride gave the dimethyl ketone **28** which was converted to the corresponding tosylhydrazone **29** by treatment with *p*-toluenesulfonylhydrazide in methanol.


O
a
O
b
H
17
18
O
c
O
d
H
SC4H9
H
SC4H9
19
20
CH3O
OCH3
O
e
CH3O
OCH3
O
f
H
SC4H9
H
21
22

Scheme 2

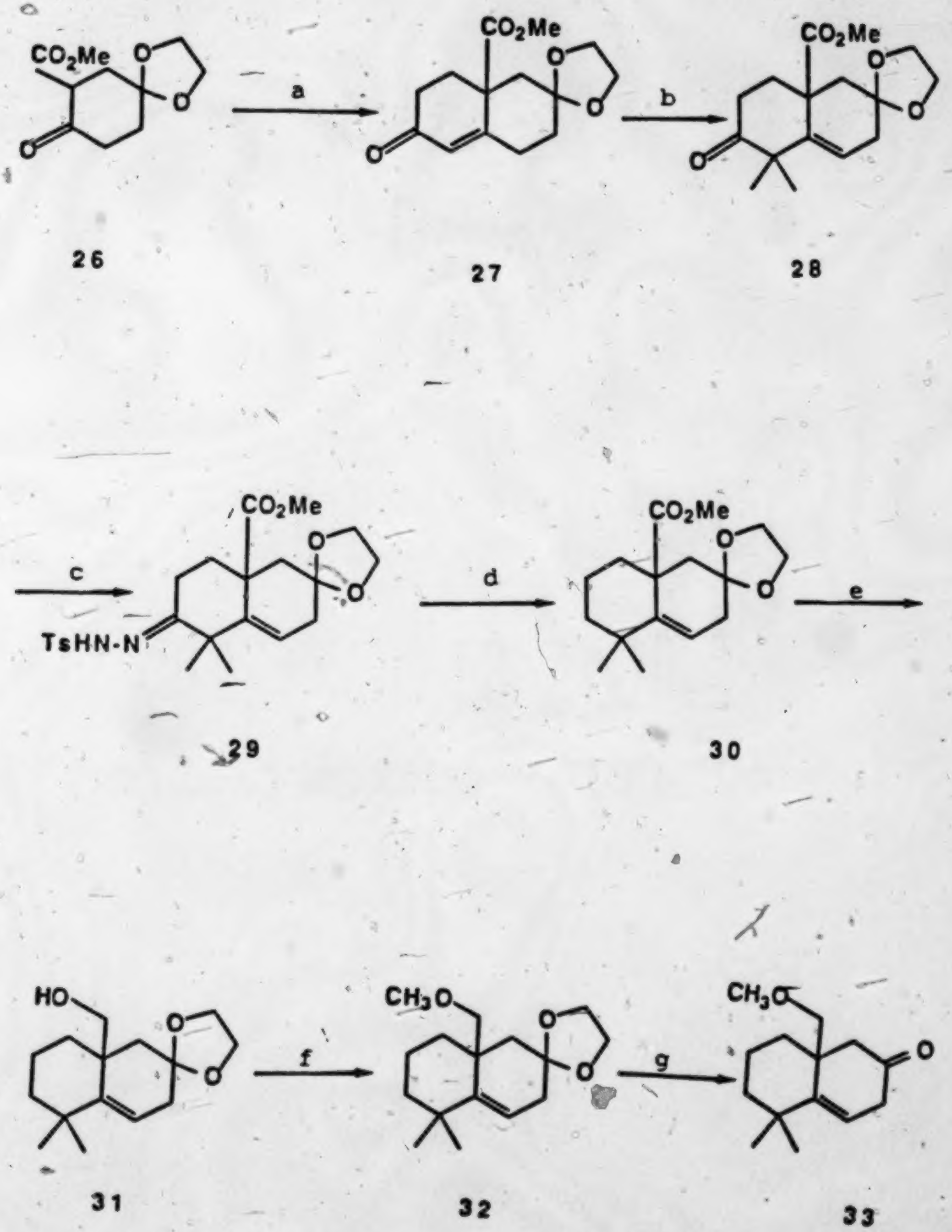
Scheme 2 (contd)



a) vinylmagnesium chloride, tetrakis[iodo(tri-*n*-butylphosphine)]copper(I); b) HCOOEt, NaOMe, *n*-BuSH; c) NaH, DMSO, $(HCHO)_n$; d) lithiated orcinol dimethylether; e) 25% aqueous KOH, diethyleneglycol, reflux; f) methylene triphenylphosphorane, DMSO, THF; g) NaSEt, DMF, 100°C; h) *p*-TSOH, benzene reflux.

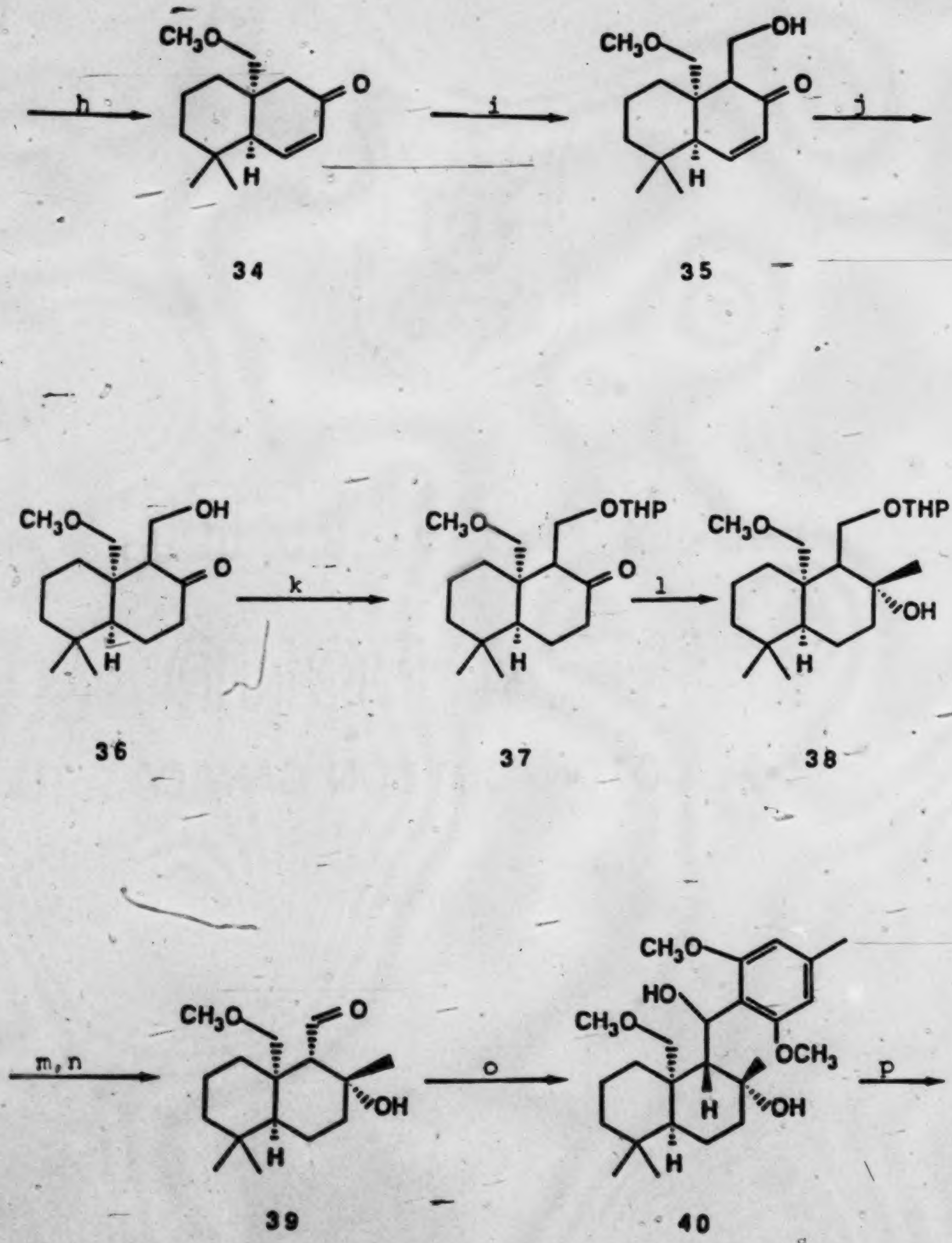
Reduction of **29** with sodium cyanoborohydride resulted in the formation of ester **30**. On further reduction with lithium aluminum hydride, **30** was converted to the alcohol **31**. The hydroxyl group was smoothly converted to the corresponding methyl ether on treatment with methyl iodide in the presence of sodium hydride. Transacetalization of compound **32** thus obtained, with acetone in the presence of *p*-toluenesulfonic acid resulted in the formation of ketone **33**. The compound **34** with the required *cis*-stereochemistry was formed by isomerising the double bond of **33** using basic conditions. Formylation followed by hydrogenation led to the formation of keto alcohol **36**. On treatment with dihydropyran and a catalytic amount of *p*-toluenesulfonic acid, this compound was converted to tetrahydropyranyl ether **37**. Addition of methyllithium to **37** resulted in the tertiary alcohol **38** which was transformed to aldehyde **39** by selective hydrolysis of the acetal group with pyridinium *p*-toluenesulfonate followed by oxidation with pyridinium chlorochromate. Coupling of aldehyde **39** with the lithium salt of orcinol dimethyl ether gave alcohol **40** which was cyclised to ether **41** on treatment with pyridinium chloride. Compound **41** now has the A, B, D and E rings of siccanin. However the stereochemistry at C-9 is opposite to that found in the natural product. Selective demethylation with sodium ethanethiolate in refluxing *N,N*-dimethylformamide gave the phenolic compound **42**. Isomerisation at C-9 and formation of the D ring were effected simultanously, when compound **42** was exposed to boron trifluoride etherate, to yield the desired siccanin methyl ether **43**, albeit in low yield. Final conversion of **43** to siccanin was accomplished by treatment with sodium ethanethiolate in refluxing *N,N*-dimethylformamide.

Several years ago it was observed in our laboratory that, unlike its parent compound 4,4-dimethyl-2-cyclohexenone (**44**) which could not be effectively used as a dienophile in Diels-Alder reaction, 2-carbomethoxy-4,4-dimethyl-2,5-cyclohexadien-1-one (**45**)[23-25] possesses excellent dienophilicity. Its Diels-Alder reaction with a variety of 1,3-butadienes proceeded smoothly to give highly functionalised *cis*-fused decalin systems with a high degree of regioselectivity and stereoselectivity. It was further observed, in connection with a model study on the synthesis of limonin (**46**), that the Diels-Alder reaction of **45** with 1-vinylcyclohexene (**47**), a 1,2-disubstituted 1,3-butadiene, gave rise to adduct **48**[25] possessing the all-*cis* stereochemistry as the only product. Extrapolation of these results suggests that the addition of dienone ester **45** to a suitably protected *trans*-3-methyl-2,4-pentadien-1-ol (**49**) would give rise to adduct **50** as shown in the retrosynthetic scheme (Scheme 4). Thus, the sesquiterpene unit of siccanin could, in principle, be installed by a single reaction with complete control of the stereochemistry. Subsequent modifications of the existing functionalities by an array of rather standard reactions would lead to aldehyde **51**.

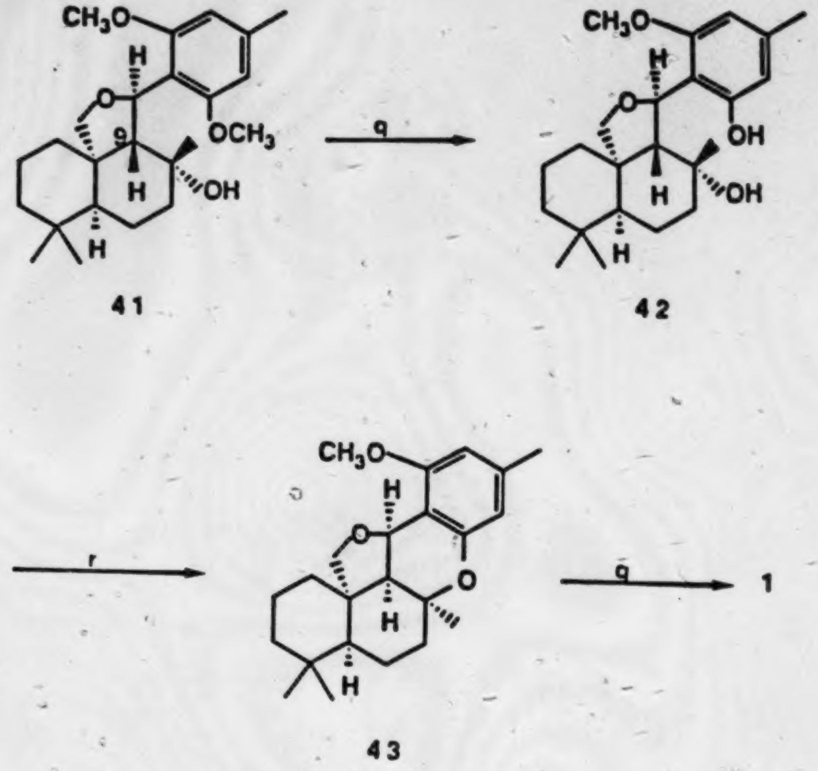


Scheme 3

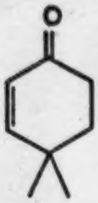
Scheme 3 (contd)



Scheme 3 (contd)



a) M.V.K, NaOMe, MeOH; b) MeI, *t*-BuOK, *t*-BuOH; c) $TsNHNH_2$, MeOH; d) $NaB(CN)H_3$, *p*-TsOH, Sulfolane, DMF, 100°C; e) LAH, DME; f) MeI, NaH, DME; g) *p*-TsOH, acetone, 25°C; h) *p*-TsOH, MeOH, 50°C; i) LDA, DME, -78°C, HCHO(g); j) H_2, 10% Pd-C, EtOH; k) DHP, PPTS, CH_2Cl_2; l) ex. MeLi, Et_2O; m) PPTS, moist EtOH, 60°C; n) PCC, CH_2Cl_2; o) lithiated orcinoldimethylether, DME, -75°C - 0°C; p) Py.HCl, CH_2Cl_2; q) NaH, EtSH, DMF, 100°C; r) $BF_3.OEt_2$, CH_2Cl_2, 25°C.



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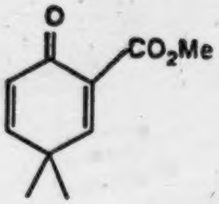

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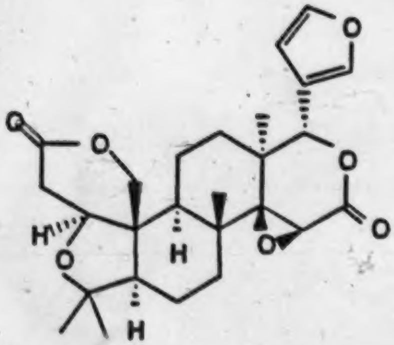

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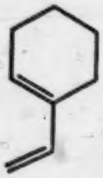

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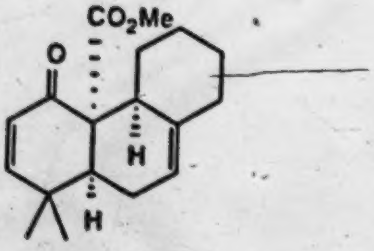

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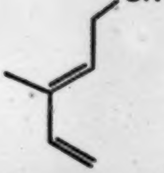

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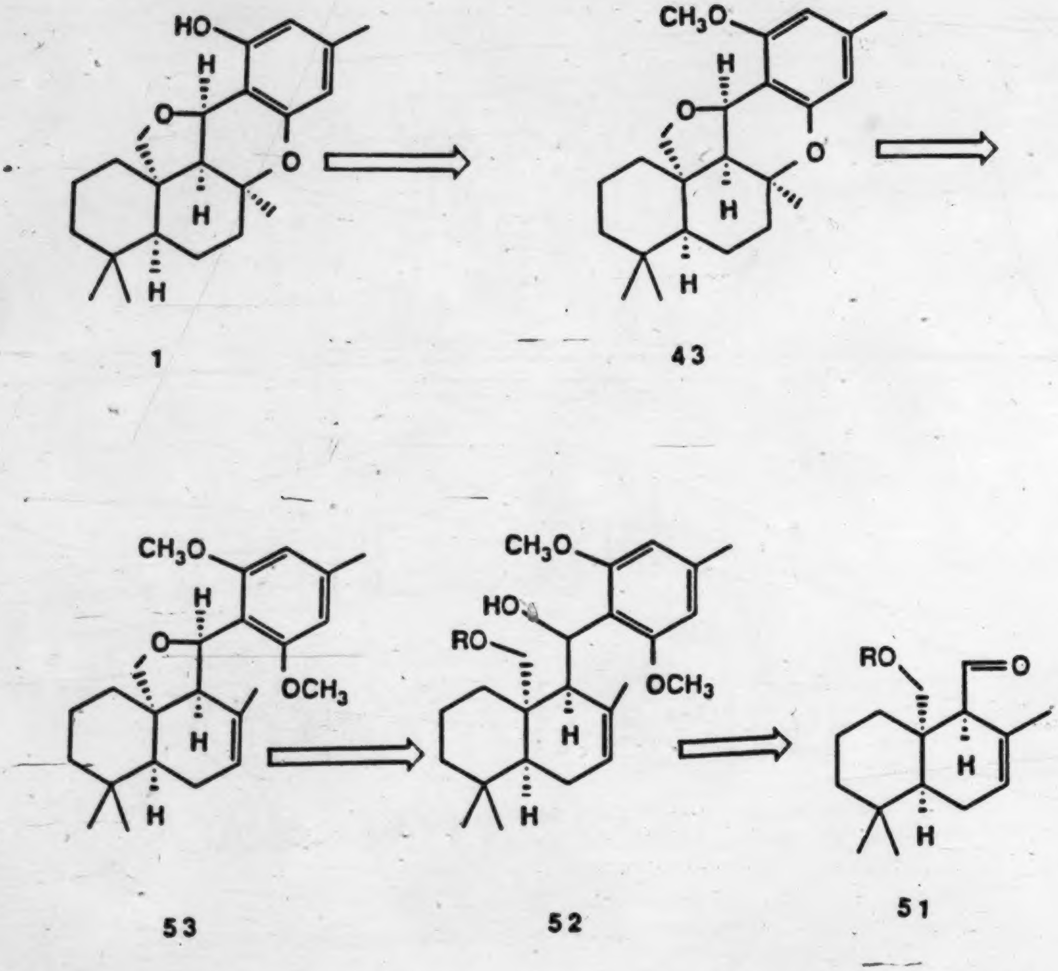
Introduction of the orcinol dimethyl ether moiety (**51**→**52**) by a Grignard reaction followed by two consecutive ether ring closures (**52**→**53**→**43**) should result in the formation of siccanin methyl ether (**43**), the immediate synthetic precursor of siccanin (**1**). Based on this synthetic approach the studies on the total synthesis of siccanin have been carried out, cumulating in the total synthesis of the methyl ether of a diastereomer which we name as isosiccanin (**54**). The experimental results are discussed in this thesis.


HO
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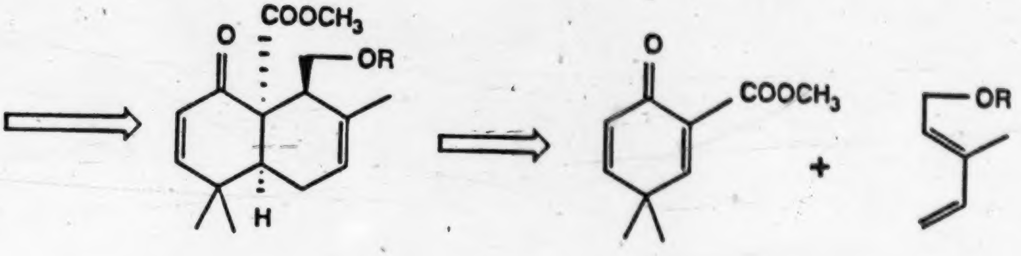
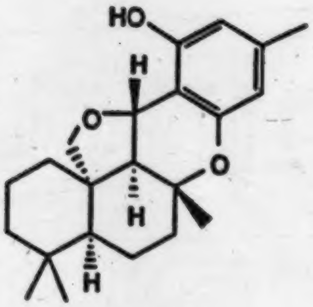
O
O
H
H
1
CH3O
H
O
O
H
H
43
CH3O
H
O
OCH3
H
H
53
CH3O
HO
RO
OCH3
H
H
52
RO
O
H
H
51

Scheme 4

Scheme 4 (contd)



50 45 49



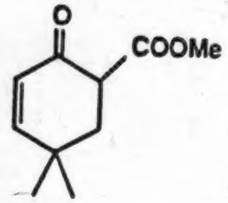
54

RESULTS AND DISCUSSIONS

The known dienone ester **45** was prepared from isobutyraldehyde in four steps in an overall yield of ca 30% in accordance with the reported procedure.[23,27] Thus treatment of *n*-Isobutenylpiperidine, readily prepared by the acid catalysed condensation of isobutyraldehyde and piperidine, with one equivalent of methyl vinyl ketone at room temperature gave enone **44**. Carbomethoxylation of **44** with dimethyl carbonate and sodium hydride in refluxing 1,2-dimethoxyethane afforded keto ester **55** which was oxidised with selenium dioxide in *t*-butyl alcohol in the presence of acetic acid to give dienone ester **45**.

Benzyl ether **56** was chosen as the counterpart for the initial Diels-Alder reaction in light of the fact that the benzyl protecting group is generally stable under acidic and basic conditions and yet can be easily removed under specific conditions such as hydrogenolysis and dissolving metal reduction. This compound was prepared from *trans*-2-buten-1-ol by a synthetic sequence shown in Scheme 5.[28]

Treatment of the alcohol with triethyl orthoacetate in the presence of a trace amount of propionic acid at 138°C for 2 hours, using a Dean-Stark apparatus to collect ethyl alcohol formed during the reaction, afforded ethyl 3-methyl-4-pentenoate (**57**) in 72% yield. Allylic bromination of **57**



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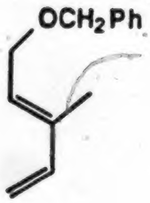


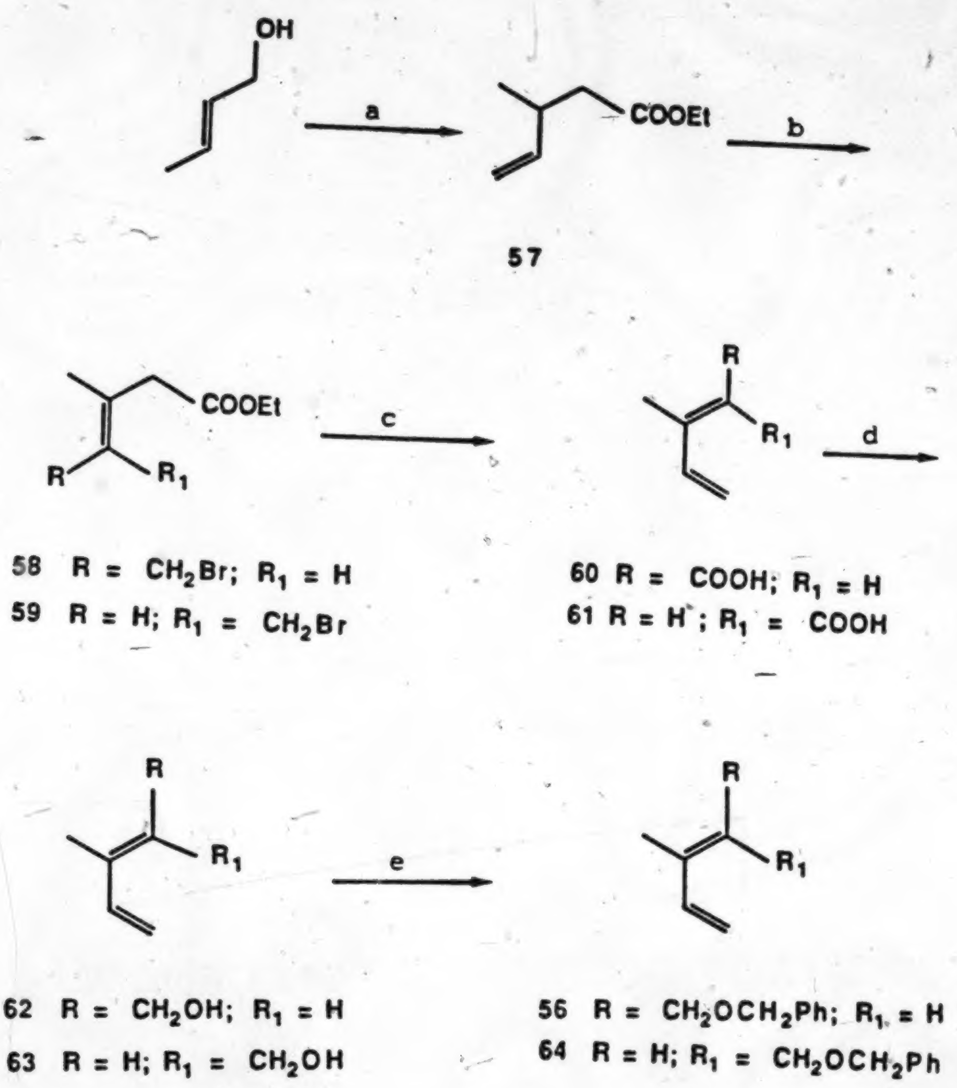
56

with *N*-bromosuccinimide in refluxing carbon tetrachloride for 3 hours using azobisisobutyronitrile as a radical initiator gave a mixture of two geometric isomers **58** and **59** in 4:3 ratio in 75% yield.

Treatment of bromo-esters **58** and **59** with sodium hydroxide in refluxing methanol for 24 hours resulted in concommitant dehydrobromination and hydrolysis to give acids **60** and **61** (3:1) in a total yield of 80%. The mixture showed, in the ir spectrum, two broad absorption bands, one in the region of 3300-2700 cm^{-1} and the other at 1700 cm^{-1} indicating the presence of the carboxyl group. In the mass spectrum, the compound showed a molecular ion peak at 112.0523 in agreement with the required molecular formula $C_6H_8O_2$. In the ^1H nmr spectrum of the mixture, multiplets at ∂ 7.84, 6.48 and 5.80 were attributed to the vinylic protons,and the methyl signals were observed at ∂ 2.30 and 2.00 in a 3:1 ratio for the *trans* and *cis* isomers respectively.

The mixture of acids **60** and **61**, without separation, was treated with lithium aluminum hydride at 0°C for 3 hours using ether as a solvent to give, in 58% yield, an isomeric mixture of alcohols **62** and **63**. The ir spectrum of the mixture showed a strong absorption at 3470 cm^{-1} due to the hydroxyl group. A molecular ion peak at 98.0728 in the mass spectrum confirmed the molecular formula $C_6H_{10}O$. In the ^1H nmr spectrum, two sets of peaks were observed in a 3:1 ratio. The major set due to the *trans* isomer **62** consisted of signals at ∂ 6.76 (dd, 3/4H, J = 12, J' = 6 Hz, $-C\mathbf{H}{=}CH_2$), 5.63 (t, 6/4H, J = 7 Hz, $=CH_2$), 4.25 (d, 6/4H, J = 7 Hz, $=CH-C\mathbf{H}_2OH$) and 1.75 (d, 9/4H, J = 1 Hz, $-CH_3$), whereas the minor set of signals, attributed to the *cis* isomer **63**, appeared at ∂ 6.74 (dd, 1/4H, J = 10, J' = 6 Hz, $-C\mathbf{H}{=}CH_2$), 5.62 (t, 2/4H, J = 7 Hz, $=C\mathbf{H}_2$), 4.21 (d, 6/4H, J = 7 Hz, $=CH-C\mathbf{H}_2OH$) and 1.80 (d, 3/4H, J= 1Hz, $=C-CH_3$).

Benzylation of the alcohols **62** and **63** with benzyl bromide and sodium hydride in tetrahydrofuran at room temperature for 8 hours gave **56** along with its cis isomer **64** in 3:1 ratio in 83% yield. The spectral properties of the mixture were found to be consistent with the structural assignment. Thus, a molecular ion peak at 187.1124 in the mass spectrum confirmed the molecular formula $C_{13}H_{16}O$. The ir spectrum showed an absorption at 1600 cm^{-1} characteristic of the conjugated diene system and the phenyl ring. In the ^1H nmr spectrum, two sets of peaks were observed; the major set due to the *trans* isomer **56**, consisted of signals at ∂ 6.40 (dd, 3/4H, J = 12 , J' = 6 Hz, $=C\mathbf{H}H$), 1.74 (d, 9/4H, J = 1 Hz, $=C-C\mathbf{H}_3$). Whereas the minor set of signals attributable to the *cis* isomer **64** appeared at ∂ 6.68 (dd, 1/4H, J = 10, J' = 4 Hz, $=C\mathbf{H}H$), 1.86 (d, 3/4H, J = 1 Hz,$-CH_3$). In addition, common signals were found at ∂ 7.30 (m, 5H, aromatic); 4.52 (s, 2H, benzylic); 5.16 (2H, d, J= 8hz, $-C\mathbf{H}_2OCH_2Ph$). The desired *trans*-diene **56** was not separable from its cis-isomer **64**. Inasmuch as the former was found to react preferentially, the mixture of the two isomeric dienes was used.



58 R = CH_2Br; R_1 = H

59 R = H; R_1 = CH_2Br

60 R = COOH; R_1 = H

61 R = H ; R_1 = COOH

62 R = CH_2OH; R_1 = H

63 R = H; R_1 = CH_2OH

56 R = CH_2OCH_2Ph; R_1 = H

64 R = H; R_1 = CH_2OCH_2Ph

a) $CH_3C(OEt)_3$, CH_3CH_2COOH, 138°C; b) NBS, AIBN, CCl_4, reflux; c) NaOH, MeOH, reflux; d) LAH, Et_2O, R.T; e) NaH, $PhCH_2Br$, THF, R.T.

Scheme 5

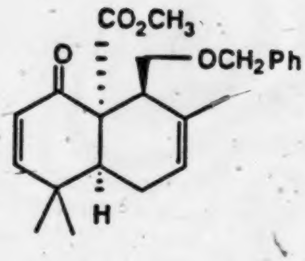
The Diels-Alder addition of dienone ester **45** to diene **56** was initially carried out at -40°C in ether using 2 equivalents of the 3:1 mixture of **56** and **64** and 0.5 equivalent of anhydrous ferric chloride as a catalyst. The reaction was found to be extremely slow. Even after 4 days, 70% of the dienophile remained unreacted. When the reaction was carried out at -20°C with increased amount of ferric chloride (1 equivalent), the reaction proceeded considerably more rapidly to give, after 48 hours, two products in a ratio of 8:1 and in a total yield of 92% on the basis of consumed starting dienophile **45**. The recovery of the latter compound was ca. 30% whereas the dienes were recovered to the extent of ca. 50%. The ^{1}H nmr analysis of the recovered diene mixture showed that now dienes were present in a ratio of 2:1 with the originally minor component **64** predominating. This result indicated that the *trans*-diene **56** was consumed preferentially as expected, on the basis of the known reactivity of *trans*- and *cis*-piperylene towards dienone ester **45**.[23,26]

The two products were readily separated by column chromatography on silica gel. The major compound, isolated in 84% yield, showed absorption bands in the ir spectrum at 1728 and 1688 cm^{-1} indicating respectively the presence of an ester group and an α,β-unsaturated ketone. That the former was in the form of a methyl ester was confirmed by the ^{1}H nmr spectrum which showed a sharp singlet at ∂ 3.54. Five aromatic protons were observed at ∂ 7.32 as a multiplet. A vinylic proton β to the ketone carbonyl appeared as a doublet of doublets (J = 11, J' = 2 Hz) at ∂ 6.28 , while a proton α to the ketone was observed as a doublet (J = 11 Hz) at ∂ 5.88. A broad singlet appearing at ∂ 5.68 was attributed to a proton on a trisubstituted carbon-carbon double bond and three singlets at ∂ 1.80, 1.14 and 1.10 indicated the presence of three methyl groups, one of which was vinylic. The molecular formula of $C_{23}H_{28}O_4$ was indicated by the mass spectrum which displayed a molecular ion peak at 368.1986. These spectral data together with the fact that the *trans*-diene **56** was consumed preferentially during the Diels-Alder reaction and the previous observation [25] that 1-vinylcyclohexene added to dienone ester **45** exclusively *endo* to its enone system led us to assign the structure **65** to this compound. This assignment was unambiguously confirmed at a later stage by a X-ray analysis on a derivative (*vide infra*).

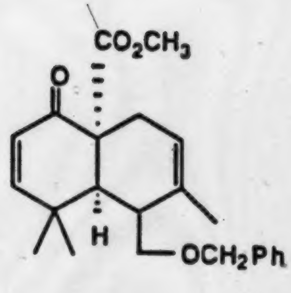
The minor product, which was isolated in 8% yield, showed in the mass spectrum a molecular ion peak at 368.1987 indicating that it is isomeric with the major product. The ir spectrum of the compound showed absorptions at 1745 and 1679 cm^{-1} indicating respectively the presence of an ester and an α,β-unsaturated ketone. The ^1H nmr spectrum displayed peaks for the conjugated enone system at ∂ 6.59 and 5.92. The broad singlet at ∂ 5.46 was assigned to a vinylic proton of the trisubstituted double bond. Methyl protons of the ester group appeared as a sharp singlet at ∂ 3.70 and the gem-dimethyls appeared at 1.18 and 1.02, each as a singlet. These spectral data further indicated that the compound is a stereoisomer or a regioisomer of the major product **65**. In order to obtain additional information, decoupling experiments were carried out. When the signal at ∂ 5.46, corresponding to the vinylic proton of the trisubstituted double bond, was irradiated, the doublet of doublets at ∂ 2.58 and 2.12 collapsed to two doublets with a coupling constant of 15 Hz each. This observation indicated to us that the vinylic proton is coupled to two geminally coupled methylene protons, which in turn do not couple with any other protons of the molecule. Consequently, structure **66** was tentatively assigned to the minor product, in which a vinylic methylene is adjacent to a quarternary centre and hence these protons should appear as two mutually coupled doublets, each with a large geminal coupling constant, upon irradiation of the vinylic proton.

Other reaction conditions were also attempted in order to facilitate the Diels-Alder addition of **45** to **56**. Changing the solvent from ether to 1,2-dimethoxyethane, which was found to dissolve the ferric chloride-dienophile complex better, neither increased the yield of **65** nor enhanced the rate of reaction. The use of dichloromethane resulted in the complete consumption of the dienophile in less than 24 hours. However, under these conditions a higher yield (ca. 40%) of the undesired isomer **66** was obtained.

After the formation of **65**, which possesses all the carbon atoms of the sesquiterpene portion of siccanin (**1**), was effected by a Diels-Alder reaction, our synthetic plan



65

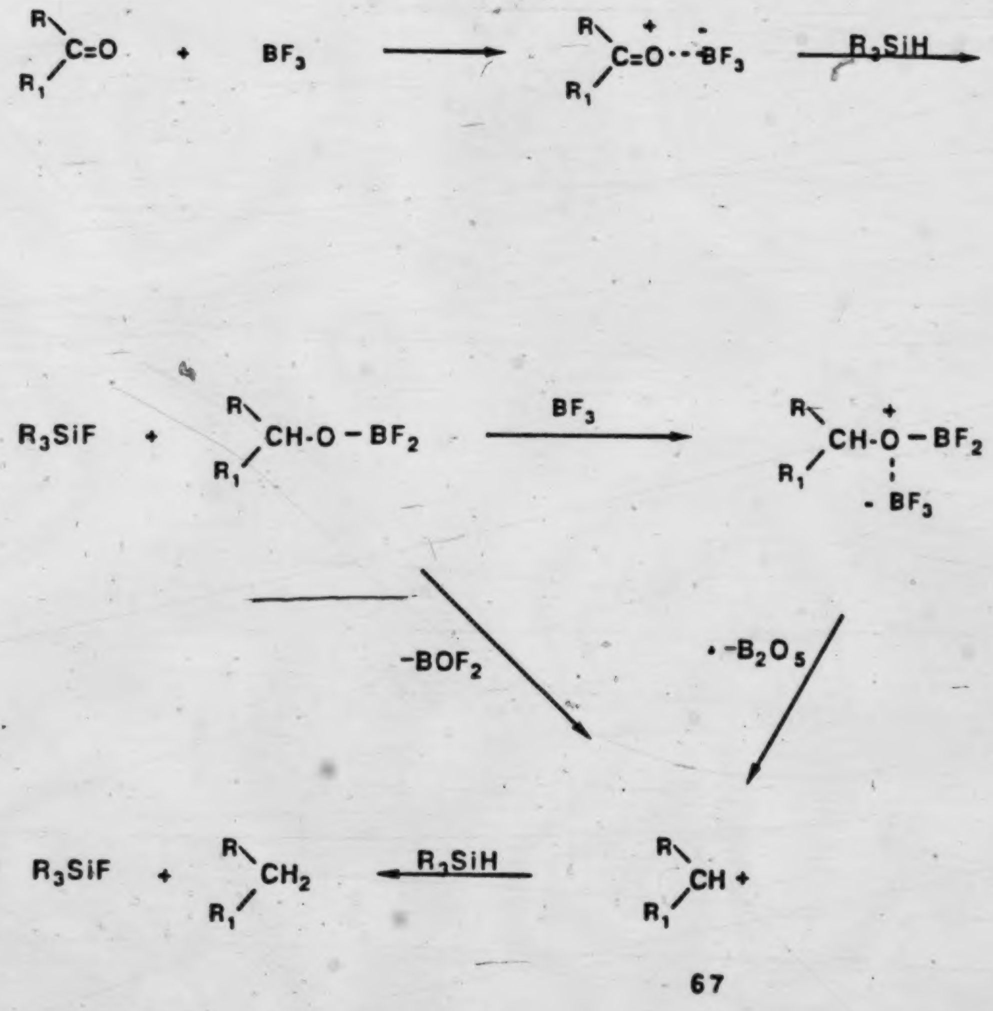


66

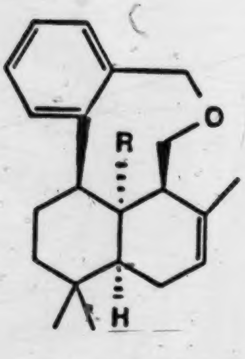
(Scheme 4) called for its conversion to a compound of type **51**. The following three operations are required: the complete removal of the enone system, the transformation of the benzyl ether to an aldehyde and that of the ester to a suitably protected alcohol. To reduce the complexity of the molecule, it is advantageous to saturate the enone moiety first. Towards this end, the reduction of the ketone carbonyl to the hydrocarbon level was first attempted. Existing direct methods such as Wolff Kishner[29] and Clemmensen[30,31] reductions are apparently not applicable to the present case since the vigorous conditions required are not compatible with the other existing functional groups.

Fry and co-workers[32] recently reported reduction of aldehydes and ketones to the corresponding hydrocarbons using organosilane in the presence of gaseous boron trifluoride. Scheme 6 outlines the proposed mechanistic rationale for this reaction. If the reduction indeed proceeds via the carbonium ion **67**, the ease of reduction of the carbonyl group of an conjugated enone system is expected due to the greater stability of an allylic carbonium ion.

On this assumption, Diels-Alder adduct **65** was treated with gaseous boron trifluroide in dicholoromethane at 0°C immediately followed by the addition of triethylsilane. After 5 minutes, a compound, which was identified as cyclic ether **68**, was formed in 40% yield. The compound showed a molecular ion peak at 354.2200 in accord with the molecular formula $C_{23}H_{30}O_3$. An intense absorption at 1725 cm^{-1} in the



Scheme 6



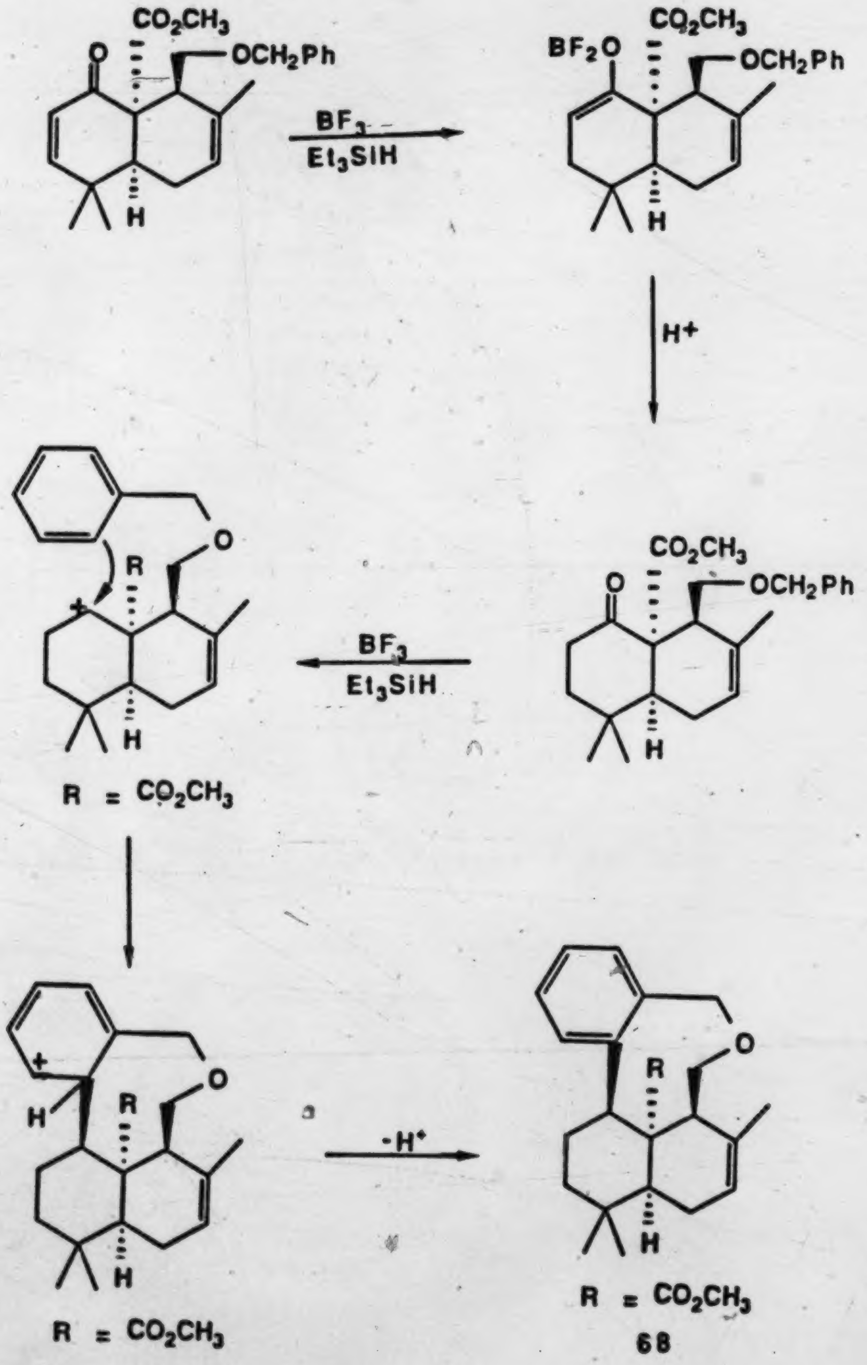
R = CO_2CH_3

68

ir spectrum suggested that the ester group was intact. Its presence was further confirmed by the ^{1}H nmr spectrum, showing a sharp singlet at ∂ 3.66. The reduction of the enone system was indicated by the absence of other carbonyl absorptions in the ir spectrum, which also displayed a band at 735 cm^{-1} indicative of an *ortho*-disubstituted benzene. These structural features were also verified by the ^{1}H nmr spectrum, showing a single vinylic proton at ∂ 5.70 as a broad singlet and only four aromatic protons as a multiplet centred at ∂ 7.00. Reduction of the conjugated carbon-carbon double bond in **65** prior to the deoxygenation followed by an intramolecular Friedel-Crafts alkylation[33] (Scheme 7) could be attributed to the formation of compound **68**.

At this point, it was decided to remove the enone system by selectively reducing its carbon-carbon double bond first. In the presence of Wilkinson's catalyst [tris-(triphenylphospine)rhodium(I) chloride],[34] hydrosilanes have been shown to add to α,β-unsaturated ketones exclusively by a 1,4-addition process to give the corresponding silyl enol ethers.[35] These silyl enol ethers can be readily hydrolysed to the corresponding ketones.[36] This approach was attempted for the selective reduction of enone **65**.

When finely divided solid keto ester **65** was suspended in triethylsilane in the presence of Wilkinson's catalyst, only a small amount of addition product was observed even after a long reaction time (4 days).


CO$_2$CH$_3$
OCH$_2$Ph
O
H
BF$_3$
Et$_3$SiH
CO$_2$CH$_3$
BF$_2$O
OCH$_2$Ph
H
H+
CO$_2$CH$_3$
OCH$_2$Ph
O
H
BF$_3$
Et$_3$SiH
O
R
+
H
R = CO$_2$CH$_3$
O
R
+
H
H
R = CO$_2$CH$_3$
-H$^+$
O
R
H
R = CO$_2$CH$_3$
68

Scheme 7

However, when enone **65** was treated with triethylsilane and a catalytic amount of Wilkinson's catalyst in benzene solution at room temperature, the starting material was consumed completely within 48 hours. The purified product obtained in quantitative yield was identified as the silyl enol ether **69**. An absorption band in the ir spectrum of the compound at 1720 cm^{-1} suggested the presence of the ester group. Its presence was further confirmed by the ^{1}H nmr spectrum showing a sharp singlet at ∂ 3.72. Furthermore, the absence of additional absorptions in the ir spectrum due to enone carbonyl suggested its reduction. Additional evidence for the assigned structure was provided by the ^{1}H nmr spectrum of the compound. A broad singlet at ∂ 5.24 was due to the vinylic proton of the trisubstituted carbon-carbon double bond, and the aromatic protons appeared as a multiplet centred at ∂ 7.30. A molecular ion peak at 484.3013 in the mass spectrum confirmed the molecular formula $C_{29}H_{44}O_4Si$.

Attempted hydrolysis of **69** with potassium carbonate in aqueous methanol was not satisfactory. Most of the starting material was recovered intact after 24 hours at room temperature. On the other hand, treatment of **69** with tetra-*n*-butylammonium fluoride in tetrahydrofuran at room temperature resulted in its quantitative conversion to the required ketone **70** in less than two hours. It was shown that the conversion of the crude silyl enol ether **69** to ketone **70** was equally facile. Thus, the large scale preparation of ketone

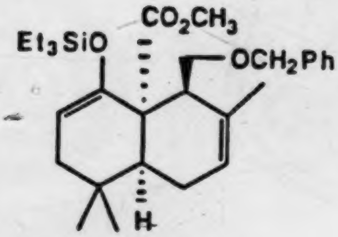
70 could be conveniently carried out in two steps from **65** without purification of the intermediate silyl enol ether.

The saturated ketone **70** showed a molecular ion peak 370.2144 in the mass spectrum, in agreement with the molecular formula $C_{23}H_{30}O_4$. In the ir spectrum, a broad and intense absorption band appeared at 1715 cm^{-1} for both the ester and ketone groups. Further proof for the designated structure came from the ^1H nmr spectrum. A singlet at ∂ 3.40 was readily attributed to the protons of the methyl ester group. The remaining methyl groups appeared at ∂ 1.82, 1.22 and 0.88, each as a singlet, whereas a vinylic proton was found at ∂ 5.30 as a broad singlet. The presence of a saturated ketone was further confirmed by the ^{13}C nmr spectrum, which showed a signal at ∂ 207.85 for the ketone carbonyl carbon as opposed to the signal at ∂ 196.094 observed for the enone carbonyl carbon in the ^{13}C nmr spectrum of **65**.

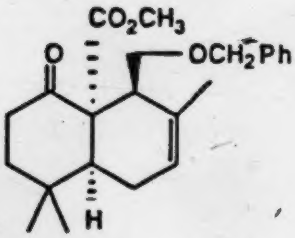
Hutchins and co-workers[37] have reported the selective conversion of aldehydes and ketones to hydrocarbons by reduction of the *p*-toluenesulfonylhydrazone derivatives, prepared *in situ*, with sodium cyanoborohydride. Attempted application of this procedure to **70** proved to be fruitless. The starting material was recovered intact even after treatment with *p*-toluenesulfonylhydrazide and sodium cyanoborohydride in refluxing *N*,*N*-dimethylformamide for 24 hours.

Thioacetals, which can be normally prepared under reasonably mild acidic conditions, are known to undergo hydrogenolysis using Raney nickel.[38] Hence, ketone **70** was subjected to treatment with an excess of 1,2-ethanedithiol in the presence of boron trifluoride etherate in dicholoromethane solution.[39] The unreacted starting material was recovered, unfortunately, even after 24 hours of the reaction period. Recently, titanium tetrachloride[40] has been shown to be a superior catalyst to induce the thioacetal formation as compared to boron trifluoride etherate. In our case, however, similar results were obtained when titanium tetrachloride was employed.

Evans and co-workers[41] have reported that ketones could be readily converted to their corresponding thioacetals using alkylthiosilanes in the presence of zinc iodide. Alkylthiosilane **71** was thus prepared in 50% yield by treatment of 1,2-ethanedithiol with excess hexamethyldisilazane in the presence of a catalytic amount of imidazole under reflux[42] for 3 hours. The compound could be readily identified by its ^{1}H nmr spectrum. Two singlets at ∂ 2.6 and 0.28 were observed and could be attributed respectively to the methylene and the methyl protons (the reported shifts[42] are also ∂ 2.6 and 0.28). Unfortunately, by the use of this reagent and the reported reaction conditions,[41] the desired thioacetal derivative of **70** could not be obtained.



69



70

$(CH_3)_3$-Si-SCH$_2$CH$_2$S-Si-$(CH_3)_3$

71

In principle, the reduction of the ketone carbonyl in question could be achieved indirectly by deoxygenation of the corresponding alcohol. Thus, compound **70** was treated with sodium borohydride in methanol.[43] Disappointingly, no signs of any reaction were observed even after 6 hours at room temperature and the starting material was recovered intact. On the other hand, the use of lithium aluminum hydride as a reducing agent gave a complex mixture of products which could be neither separated nor identified. To circumvent this problem, the keto ester **70** was subjected to reduction with other reducing agents.

Reduction of the keto ester **70** with 2 equivalents of diisobutylaluminium hydride (DIBAL-H)[44] in an etheral solution at 0°C furnished in 61% yield a 2:1 mixture of two diastereomeric alcohols **72** and **73**, which could be separated by flash column chromatography.[45] In the ir spectra, the major product **72** showed absorptions centred at 3350 and 1717 cm^{-1} due to a hydroxyl and an ester carbonyl respectively. The presence of a methyl ester function was further confirmed by the ^1H nmr spectrum showing a singlet at ∂ 3.64. The remaining methyl groups appeared at ∂ 1.86, 1.18 and 0.96, each as a singlet. The vinylic proton appeared as a broad singlet at ∂ 5.32. A multiplet at ∂ 3.78 was assigned to the methine proton adjacent to the hydroxyl group and the benzylic protons appeared as two mutually coupled doublets at ∂ 4.46 and 4.40 with a coupling constant of 12 Hz. A molecular ion peak corresponding to the molecular formula $C_{23}H_{32}O_4$ appeared at 372.2293 in the mass spectrum.

The minor product **73** showed characteristic hydroxyl and ester absorptions in the ir spectrum at 3675 and 1705 cm^{-1} respectively. The ^1H nmr spectrum displayed four methyl singlets at ∂ 3.58, 1.84, 0.92 and 0.84, a broad singlet at ∂ 5.42 for the vinylic proton and a multiplet at ∂ 3.6 for the methine proton adjacent to the hydroxyl group. A molecular ion peak at 372.2292 in the mass spectrum confirmed the molecular formula $C_{23}H_{32}O_4$.

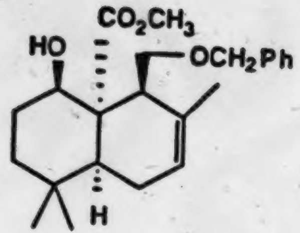
Comparison of the spectral data of the two compounds suggested that they are epimeric at the newly generated chiral centre. The spectral data however did not allow unambiguous assignment of stereochemistry to each of these compounds. The assignment of stereochemical formula **72** to the major compound and that of **73** to the minor isomer were based on the following experimental results. Treatment of ketone **70** with a large excess of DIBAL-H (5 equivalents) at room temperature for 5 hours resulted in the predominant formation of the diol **74** (75% yield). This compound was also obtained later by a different reaction and identified unambiguously by an X-ray analysis (*vide infra*). Since diol **74** was formed predominantly from extended reduction of the ketone **70**, logically the major product from the limited reduction of the later compound should possess stereochemistry as shown in **72**. It follows that the minor product should possess stereochemistry as shown in **73**. The preferential formation of alcohol **72** could be rationalised by invoking initial complexation of the ester group with DIBAL-H [46,47] followed by an intramolecular delivery of a hydride ion from the *re*-face [48] of the molecule as depicted in **75** and **76**.

The reduction of ketone **70** was also attempted using bulkier reducing agents such as lithium tri-*t*-butoxyaluminium hydride[49] and potassium tri-*s*-butylborohydride[50] in order to increase the stereoselectivity. However, in both cases, no detactable amounts of the expected products were obtained and the starting material was recovered unchanged.

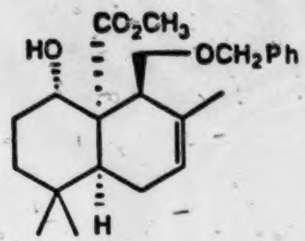
Several deoxygenation methods were tried on alcohols **72** and **73**. It is well known that the sulfonates of simple alcohols can be reduced to the corresponding hydrocarbons with lithium aluminium hydride,[51a-d] sodium cyanoborohydride,[52a-c] and triethylborohydride.[53a-d] In addition to these metal hydride reductions, additional methods such as electrolysis[54] and reduction with zinc dust and sodium iodide in polar a solvent[55] are also known to be effective. Thus the preparation of methanesulfonates from alcohols **72** and **73** was attempted. However, when the mixture of alcohols were treated with methanesulfonyl chloride and triethylamine[56] at room temperature for 12 hours, no reaction was observed.

An alternative method for deoxygenation of alcohols involves dehydration followed by hydrogenation. When the mixture of epimeric alcohols **72** and **73** was subjected to dehydration with phosphorous oxychloride in refluxing pyridine[57] for 8 hours, the major component **72** was converted to olefin **77**, while the minor isomer **73** was found to be unreactive. When pure alcohol **72** was subjected to the dehydration reaction, olefin **77** was formed in 70% yield. The compound showed an ester carbonyl absorption in the ir spectrum at 1725 cm^{-1}. The required molecular formula $C_{23}H_{28}O_4$ was confirmed by the mass spectrum which displayed a molecular ion peak at 354.2210. In the ^{1}H nmr spectrum the aromatic protons appeared at ∂ 7.26 as a multiplet, whereas the vinylic protons appeared at ∂ 5.78 (bd, J = 6 Hz), 5.68 (m) and 5.42 (bs).In addition, four methyl singlets were observed at ∂ 3.48, 1.64, 0.80 and 0.78.

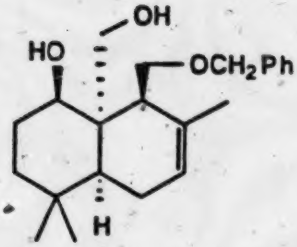
The overall yield of the olefin **77** from ketone **70** was rather low (ca. 30%) because the selective reduction (**70**→**72**→**73**) was not highly efficient and only one reduction product (**72**) could undergo dehydration. Consequently this approach was abandoned and we turned our attention to the possible modification of the diol **74**. In order to facilitate the preparation of this compound, ketone **70** was subjected to reduction with sodium bis(methoxyethoxy)aluminium hydride (Red-Al),[58] which is known to be a superb reagent for the reduction of both ketones and esters.[58a-c] When keto ester **70** was treated with an excess of Red-Al in a solution of ether and toluene at room temperature for 7 hours, two epimeric alcohols were obtained in a ratio of 8:1 and in a total yield of 80%. The major alcohol, m.p. 90-92°C, was found to be identical with that previously obtained with DIBAL-H



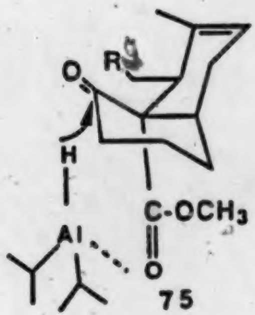
72



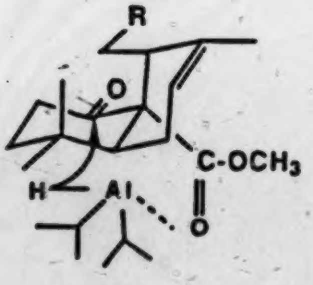
73



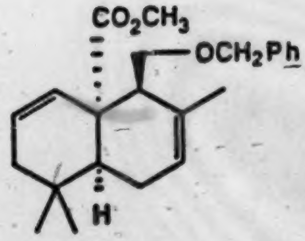
74



75



76



77

(*vide supra*). It showed a strong absorption at 3400 cm^{-1} in the ir spectrum for the hydroxyl groups and the absence of any carbonyl absorption. Its molecular formula of $C_{23}H_{32}O_3$ was confirmed by the molecular ion peak at 344.2364 in the mass spectrum. In the ^1H nmr spectrum, the compound showed a multiplet at ∂ 7.32 attributed to the aromatic protons. The vinylic proton appeared as a broad singlet at ∂ 5.44. Two mutually coupled doublets ($J = 12$ Hz each) at ∂ 4.80 and 4.62 could be readily attributed to the benzylic protons. The ^1H nmr spectrum also displayed three methyl singlets at ∂ 1.76, 0.94 and 0.78. These spectral data are in agreement with the gross structure shown in **74**. The stereochemistry of the compound was unambiguously determined by a single crystal X-ray analysis. The three dimensional structure of the compound as determined by X-ray crystallography is shown in Figure 1.

The minor product was shown by the following spectral data to be a diastereomer of diol **74**; consequently, to this compound structure **78** could be readily assigned. Like **74**, the compound did not display any carbonyl absorption in its ir spectrum but a strong absorption at 3424 cm^{-1} characteristic of hydroxyl group. The mass spectrum confirmed its molecular formula $C_{22}H_{32}O_3$ showing a molecular ion peak at 344.2347. The ^1H nmr spectrum showed a multiplet at ∂ 7.30 for the aromatic protons and a broad singlet at ∂ 5.80 for a vinylic proton. The benzylic protons again appeared as doublets at ∂ 4.80 and 4.60, each with a large geminal

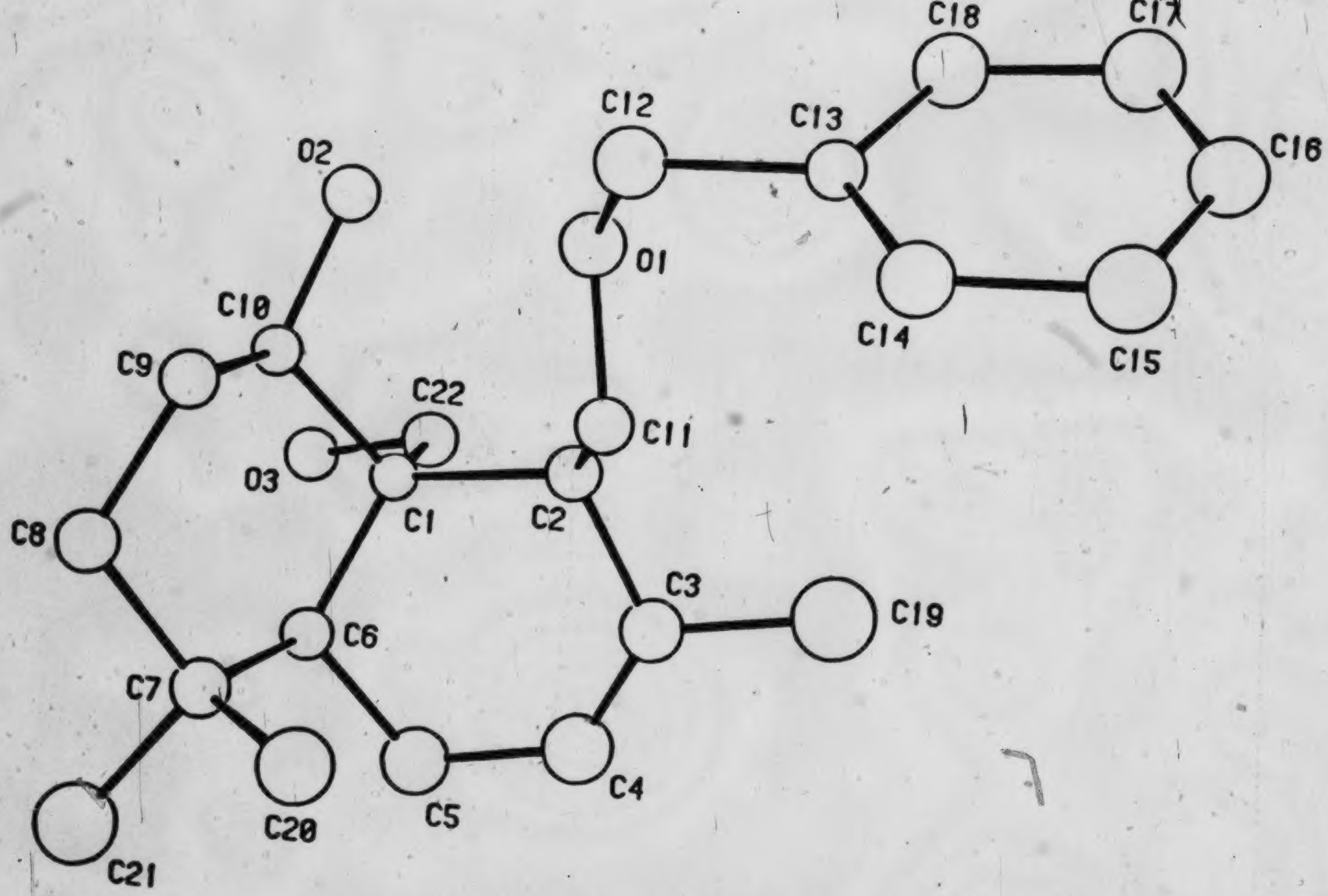


Figure 1 The three dimensional X-ray crystallographical structure of diol 74

coupling constant of 12 Hz. Characteristic methyl singlets were observed at ∂ 1.80, 0.84 and 0.76.

Selective acetylation of **74** with one equivalent of acetic anhydride in pyridine[59] afforded hydroxy acetate **79** in 77% yield. The ir spectra showed absorptions at 3420 and 1741 cm^{-1} indicating the presence of hydroxyl and ester groups.The molecular ion peak at 386.2456 in the mass spectrum confirmed its molecular formula $C_{24}H_{34}O_4$. The ^1H nmr spectrum showed a multiplet at ∂ 7.36 for the aromatic protons and a broad singlet at ∂ 5.55 for the vinylic proton. The methyl protons of the acetyl group appeared at ∂ 2.12 as a singlet. Other methyls were also observed as singlets at ∂ 1.72, 1.06 and 0.94. The large downfield shifts of two doublets at ∂ 3.70 and 3.56, corresponding to the methylene protons of the primary alcoholic group in the starting material, to ∂ 4.18 and 3.92 indicated that the selective acetylation of the primary hydroxy group has occurred.

Deoxygenation of **79** was attempted by three different methods. However, none of these were successful. It was found that alcohol **79** could not be converted to the corresponding methanesulfonate or *p*-toluenesulfonate by treatment with methanesulfonyl chloride or *p*-toluenesulfonyl chloride respectively under standard conditions using triethylamine.[56]

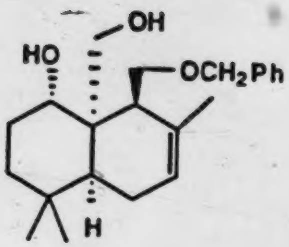
Alcohol **79** could be converted to the corresponding olefin **80** in 53% yield by dehydration using phosphorous oxychloride in refluxing pyridine.[57] The following spectral data are in agreement with the assigned structure of this compound. The ir spectrum showed an ester band at 1741 cm^{-1} and the absence of any hydroxyl absorption. In the ^{1}H nmr spectrum, a multiplet appeared at ∂ 7.36 due to aromatic protons. The three vinylic protons were assigned to the multiplet at ∂ 5.82, the doublet (J = 12 Hz) at ∂ 5.68 and the broad singlet at ∂ 5.58. The acetyl group appeared as ~~a~~ singlet at ∂ 2.08 and the three remaining methyl groups were assigned to the singlets at ∂ 1.86, 1.00 and 0.84.

Although both homogeneous and heterogeneous catalytic hydrogenation can selectively hydrogenate a disubstituted carbon-carbon double bond in the presence of a trisubstituted one,[43,60] attempts made to selectively hydrogenate diene **80** were unsuccessful. With Wilkinson's catalyst under various conditions, no hydrogenation was observed and the starting material was recovered. Similar results were obtained, when diene **80** was subjected to reduction with diimide generated *in situ* from potassium azodicarboxylate and acetic acid in ethanol.[61] On the other hand, when the hydrogenation was carried out using 5% palladium on carbon as a catalyst, under no conditions was the preferential reduction of the less substituted double bond observed.

Another procedure of deoxygenation explored, involved the conversion of alcohol **79** to the corresponding ketone **81** by treatment of the former compound with pyridinium chlorochromate[62] in dichloromethane at room temperature. Keto acetate **81** thus obtained in 78% yield showed, in the ir spectrum, carbonyl absorptions at 1745 and 1690 cm^{-1} consistent with the expected structure. In further agreement with the assigned structure, the mass spectrum displayed a molecular ion peak at 384.2296 for the required molecular formula $C_{24}H_{32}O_4$. In the ^{1}H nmr spectrum aromatic protons appeared as multiplets centred at ∂ 7.30, whereas the vinylic proton was observed as a broad singlet at ∂ 5.56. The ^{1}H nmr spectrum also displayed methyl singlets at ∂ 2.02, 1.82, 1.00 and 0.82

Although ketone **81** could be obtained in respectable yield, neither the attempted conversion to the corresponding thioacetal derivative using 1,2-ethanedithiol in the presence of titanium tetrachloride[40] nor its treatment with *p*-toluenesulfonylhydrazide and sodium cyanoborohydride in sulfolane[37] resulted in the desired product. In the former case, the starting material was recovered intact and, in the latter case, a complex mixture was produced.

Another route investigated for the removal of the enone system in **65** was via the intermediacy of the diol **82**. This compound was obtained as a single isomer in 74% yield from the reduction of **65** with Red-Al in ether and toluene at room temperature. The compound showed a strong hydroxyl absorption band at 3400 cm^{-1}. In the ^{1}H nmr spectrum, the aromatic protons were observed at ∂ 7.28 as a multiplet. Vinylic protons appeared at ∂ 5.56 (dd, J = 8, J' = 2 Hz), 5.40 (bs) and 5.26 (dd, J = 8, J' = 1 Hz). The benzylic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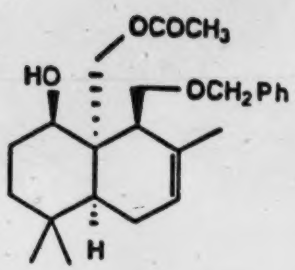
HO
OCH2Ph
H

78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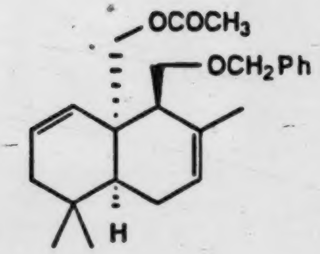
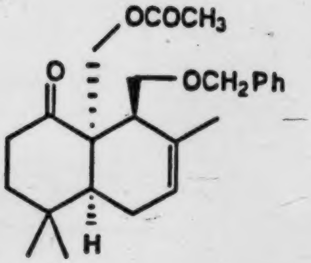
HO
OCH2Ph
H

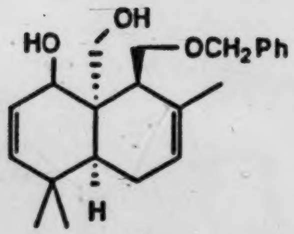
79


OCOCH3
OCH2Ph
H

80


OCOCH3
O
OCH2Ph
H

81


OH
HO
OCH2Ph
H

82

protons were assigned to the doublets at ∂ 4.48 and 4.38 (J = 12 Hz each). Three singlets were also observed at ∂ 1.78, 0.92 and 0.82 due to the three methyl groups. Although the structure of the diol **82** was clearly indicated by the spectral data, its stereochemistry at the newly generated chiral centre cannot be unambiguously assigned.

Before any attempts to remove the secondary hydroxyl group present in **82**, it is essential to protect the primary one. When **82** was treated with chloromethyl methyl ether[63] in pyridine, the expected hydroxy ether was not formed even after 12 hours at reflux. Addition of 4-(*N,N*-dimethylamino)pyridine[64] also failed to catalyse the reaction. However, the use of a strong base, sodium hydride, in 1,2-dimethoxyethane resulted in the formation of the desired compound **83** in a respectable yield of 60%. The following spectral data recorded for the compound are consistent with the assigned structure. A molecular ion peak at 386.2346 in the mass spectrum confirmed the molecular formula $C_{24}H_{34}O_4$. An absorption at 3440 cm^{-1} in the ir spectrum indicated the presence of a hydroxyl group. Aromatic protons were observed as a multiplet at ∂ 7.32 in the ^1H nmr of **83**. Vinylic protons appeared at ∂ 5.70 (m), 5.48 (bs) and 5.30 (dd, J = 10, J' = 2 Hz). The methylene protons between the two oxygen atoms were assigned to a singlet at ∂ 4.48 and the corresponding methoxy protons appeared at ∂ 3.56 as a singlet.

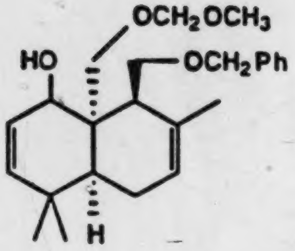
In order to remove the hydroxyl group of **83**, its conversion to the methanesulfonate and *p*-toluenesulfonate derivatives was attempted. Under various conditions however the desired derivatives could not be formed.

A successful route leading to a desirable synthetic intermediate was eventually carried out as follows. The diol **74** was subjected to treatment with a calculated quantity of chloromethyl methyl ether in the presence of excess sodium hydride at room temperature for 30 minutes, a mixture of five compounds were obtained. These products were readily separated by flash column chromatography[45] on silica gel. The major product obtained in 59% yield was identified as the cyclic acetal **84**. Its mass spectrum showed a molecular ion peak at 356.2355 suggesting a molecular formula $C_{23}H_{32}O_3$. The ir spectrum showed the absence of any hydroxyl absorption bands. In the ^1H nmr spectrum, a multiplet at ∂ 7.32 and a broad singlet at ∂ 5.34 were respectively assigned to the aromatic and vinylic protons. The two doublets, each with a coupling constant of 6 Hz, appearing at ∂ 5.12 and 4.80 were assigned to the methylene protons adjacent to the two oxygen atoms. Three methyl groups appeared at ∂ 1.81, 0.86 and 0.78. These observations are consistent with the structure **84** assigned to the compound.

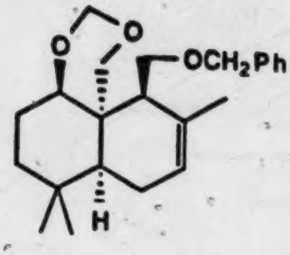
The second major product, obtained in 25% yield, was found to be the desired hydroxy ether **85** which showed a hydroxyl absorption at 3460 cm^{-1} in the ir spectrum. The ^1H nmr spectrum showed signals at ∂ 7.32 (m) for the aromatic protons and at ∂ 5.49 (bs) for the vinylic proton. The methylene protons adjacent to the two oxygen atoms appeared as two doublets with a coupling constant of 7 Hz each at ∂ 4.58 and 4.54, whereas the methoxy protons appeared at ∂ 3.32 as a singlet. The required molecular formula $C_{24}H_{36}O_4$ was confirmed by the mass spectrum which displayed a molecular ion peak at 388.2614.

Three additional products were also isolated and identified as ether **86** (10% yield), acetal **87** (7% yield), and alcohol **88** (5% yield). The structure of these compounds were also readily elucidated on the basis of their respective spectral data. Ether **86** showed the complete absence of hydroxyl absorptions in the ir spectrum. In the ^1H nmr spectrum, the compound showed two methylene singlets at ∂ 4.62 and 4.52, and two methyl singlets at ∂ 3.36 and 3.34 strongly indicating the presence of two methoxymethoxy groups. Although the mass spectrum of the compound did not show the expected molecular ion peak, a fragment resulting from the loss of a methoxymethoxy unit and a methoxymethyl unit was observed at m/z 326.2247. Further support for the required molecular formula $C_{26}H_{40}O_5$ was provided by the chemical ionization mass spectrum which indicated its molecular weight of 432.

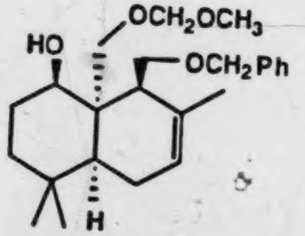
The ir spectrum of compound **87** showed no absorption due to hydroxyl group. The mass spectrum displayed a molecular ion peak at 356.2344 indicating a molecular formula of $C_{23}H_{32}O_3$. In the ^1H nmr spectrum, the methylene group flanked by two oxygen atoms appeared at low field of ∂ 5.15 and 4.84 (d, J = 6 Hz each). The presence of two vinylic



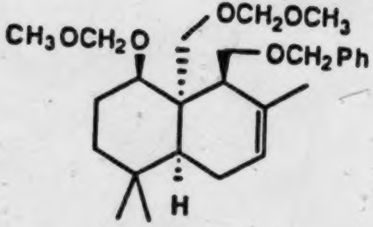
83



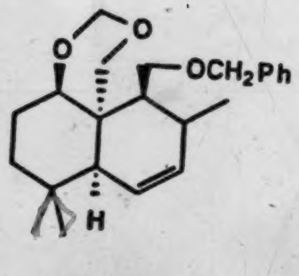
84



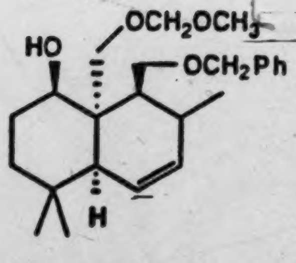
85



86



87



88

protons was indicated by two multiplets at ∂ 5.52 and 5.40. The ^1H nmr spectrum also showed the presence of three methyl groups, with two singlets at ∂ 0.99 and 0.74 and a doublet at ∂ 1.19 (J = 7 Hz). The appearance of two vinylic signals and a methyl doublet strongly suggested that the double bond had migrated to the indicated position during the reaction.

The mass spectrum of the fifth product displayed a molecular ion peak at 388.2806 indicating that a single methoxymethyl unit was incorporated and this was further verified by the ir spectrum which showed a hydroxy absorption at 3480 cm^{-1}. The presence of disubstituted double bond was suggested by the ^1H nmr spectrum showing two multiplets at ∂ 5.56 and 5.38 for two vinylic protons. At the same time a methyl doublet (J = 6 Hz) was observed at ∂ 1.13. These spectral data were in agreement with the proposed structure **88**.

The formation of compounds **84**, **87** and **88** is rather surprising. The acetal formation and the migration of carbon-carbon double bond are normally induced under acidic conditions, in sharp contrast to the basic reaction conditions applied. Furthermore, the desired product **85** was shown to be rather stable and could be stored at room temperature for a long period of time without deterioration.

In an improved procedure for the preparation of the desired hydroxy ether **85**, the diol **74** was treated with an excess of potassium hydride and 1 equivalent of chloromethyl methyl ether at -10°C for 10 minutes. Under these conditions, the desired product **85** could be obtained in a yield of 72%, along with a small amount of the disubstitution product **86**; no traces of **84**, **87** and **88** were detected. This set of reaction conditions was found to be crucial in order to produce the desired ether **85** in high yield. When the reaction was carried out either at room temperature or using bromomethyl methyl ether as an alkylating agent, acetal **84** was formed as the sole product.

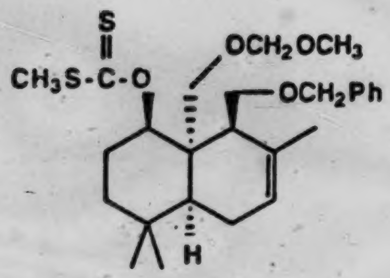
Ireland and co-workers[65] have reported a method for the deoxygenation of alcohols via the *N,N,N',N'*-tetramethylphosphorodiamidate derivatives which have been shown to give high yields of the corresponding hydrocarbons when subjected to dissolving metal reduction. *N,N,N',N'*-Tetramethylphosphorodiamidates are normally prepared by treatment of the lithium alkoxides with *N,N,N',N'*-tetramethyl phosphorodiamidochloridates in the presence of *N,N,N',N'*-tetramethylethylenediamine. For hindered alcohols, *N,N*-dimethylphosphoroamidic dichloridate was found to be a superior reagent to induce the phosphorylation and the resulting monochloride could be readily converted to the corresponding *N,N,N',N'*-tetramethylphosphorodiamidate by quenching with an excess of anhydrous *N,N*-dimethylamine.[66] The transformation of hydroxy ether **85** to its *N,N,N',N'*-tetramethylphosphorodiamidate derivative was attempted. Unfortunately neither of the described procedures could be applied sucessfully. Under various conditions, the starting material was recovered unchanged.

In another well known procedure for deoxygenation, Barton[67] has demonstrated that on reduction with tri-*n*-butylstannane, *S*-alkyl xanthates, readily prepared from the corresponding alcohols, undergo smooth reductive cleavage of the carbon-oxygen bond. It has also been demonstrated that the systems which are closely related to xanthates such as thionobenzoates,[67,70] thiocarbonyl imidazole,[67,71] thioformates,[68] and phenoxy thionocarbonate[69] also undergo reductive cleavage of the carbon-oxygen bond on treatment with tri-*n*-butylstannane. Application of such a reaction to **85** could effect its deoxygenation.

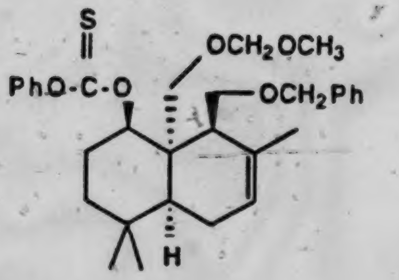
Treatment of the alcohol **85** with carbon disulfide, methyl iodide and sodium hydride in tetrahydrofuran at room temperature yielded the required *S*-methyl xanthate **89** in 32% yield. To our delight, when the solvent was changed to 1,2-dimethoxyethane, the yield of the desired product was increased dramatically to 93%. Surprisingly, when the reaction was carried out under similar conditions in 1,2-dimethoxyethane using potassium hydride as a base instead of sodium hydride, the starting alcohol was recovered without any apparent formation of xanthate **89**. The ir spectrum of **89** displayed no absorptions due to hydroxyl group, but a strong band at 1223 cm^{-1} due to carbon-sulfur double bond indicating the incorporation of the xanthate moiety. Further support for the assigned structure came from the ^1H nmr spectrum which displayed a singlet at ∂ 2.50 for the methyl group attached to the sulfur atom. The methine proton adjacent to the xanthate moiety appeared as a doublet of doublets (J = 10, J' = 5 Hz) at ∂ 5.82. This observation also served as a confirmation that, in the precursor, the free hydroxy group is secondary. The required molecular formula of $C_{26}H_{38}O_4S_2$ was confirmed by the chemical ionisation mass spectrum which indicated its molecular weight to be 478.

Although *S*-methyl xanthate **89** could be obtained in high yield, attempts to synthesise the closely related phenoxythionocarbonate derivative **90** using phenoxythiocarbonyl chloride and 4-(*N,N*-dimethylamino)pyridine[69] did not lead to the formation of the desired product.

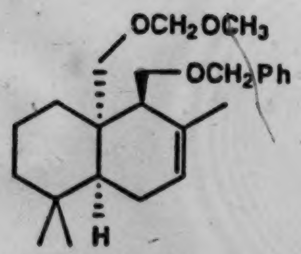
Heating xanthate **89** with tri-*n*-butylstannane and a catalytic amount of azobisisobutyronitrile in degassed toluene under an argon atmosphere at reflux temperature for 8 hours gave, in quantitative yield, the compound **91**. The mass spectrum of the compound displayed a molecular ion peak at 372.2678 in accord with the expected molecular formula $C_{24}H_{36}O_3$. Absence of absorptions due to a carbon-sulfur bond in the ir spectrum indicated the cleavage of the xanthate moiety. Further proof for the assigned structure **91** came from the ^1H nmr spectrum. A multiplet at ∂ 7.24 was readily attributed to the aromatic protons. The vinylic proton appeared at ∂ 5.38 as a broad singlet. The doublets at ∂ 4.40 and 4.36, each with a coupling of 12 Hz, were assigned to the methylene protons adjacent to the two oxygen atoms. The ^1H



89



90



91

nmr spectrum also displayed four methyl signals at ∂ 3.26, 1.66, 0.94 and 0.74.

After extensive studies, the preparation of the desired product **91** was finally achieved from the major diol **74** obtained from the reduction of the keto ester **70** (*vide supra*) in three steps: ether formation (**74** → **85**) followed by reduction of the xanthate derivative (**85** → **89** → **91**). This reaction sequence also proved to be applicable for the transformation of the minor diol **78** obtained from keto ester **70**, albeit with less efficiency.

On treatment with 1.5 equivalents of chloromethyl methyl ether in the presence of excess potassium hydride in 1,2-dimethoxyethane at -10°C, diol **78** gave rise to a mixture of two compounds **92** and **93**. The major product, obtained in 68% yield, was identified as ether **92**. Its mass spectrum showed a molecular ion peak at 432.2872 suggesting the molecular formula to be $C_{26}H_{40}O_5$. The ir spectrum of the compound showed the absence of any hydroxyl absorption bands. In the ^{1}H nmr spectrum of the compound, the aromatic and the vinylic protons were assigned respectively to the multiplet at ∂ 7.32 and the broad singlet at ∂ 5.32. Furthermore, two methylene singlets at ∂ 4.60 and 4.50 and two methyl singlets at ∂ 3.34 and 3.32 confirmed the incorporation of two methoxymethoxy groups.

The second compound, obtained in 26% yield, was found to be the desired hydroxy ether **93** which displayed hydroxyl absorption at 3400 cm^{-1} in its ir spectrum. The ^{1}H nmr spectrum showed a singlet at ∂ 4.52 for the methylene protons adjacent to two oxygen atoms. The methoxy protons appeared at ∂ 3.34 as a singlet. In addition, the ^1H nmr spectrum also showed broad singlets at ∂ 7.34 and 5.52 for the aromatic and the vinylic protons, respectively. Methyl singlets were observed at ∂ 1.80, 1.06 and 0.88. Although the molecular ion corresponding to the molecular formula $C_{24}H_{36}O_4$ was not observed in the mass spectrum, a fragment resulting from the loss of a methoxy unit appeared at m/z 326.2350.

Although the formation of compound **92** could be suppressed slightly (40% yield) using 1.2 equivalents of chloromethyl methyl ether, no appreciable change in the yield of the desired hydroxy ether **93** was accompanied. About 10% of the starting material, however, was recovered under these conditions.

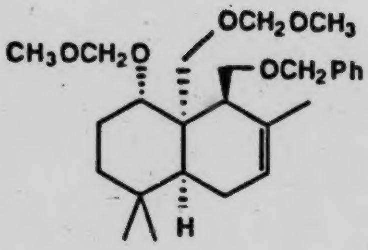
Treatment of the alcohol **93** with sodium hydride and carbon disulfide in 1,2-dimethoxyethane at room temperature followed by addition of methyl iodide gave xanthate **94** in 83% yield, after 5 hours of reaction time. The ir spectrum of **94** displayed a strong absorption band due to the carbon-sulfur double bond at 1223 cm^{-1}, indicating the incorporation of the xanthate moiety. Further support for the assigned structure came from the ^1H nmr spectrum which displayed a singlet at ∂ 2.52 for the methyl group attached to the sulfur atom. The methine proton adjacent to the xanthate moiety appeared at ∂ 6.08 as a doublet of doublet with coupling constants of 7 and 5 Hz.

Reduction of xanthate **94** with tri-*n*-butylstannane and a catalytic amount of azobisisobutyronitrile in degassed toluene under inert gas at reflux temperature for 3 hours yielded the corresponding hydrocarbon derivative **91** in quantitative yield. The compound thus obtained was found to be identical, in all respects, to that prepared previously from the major diol **74**.

The transformation of diol **78** to the desired **91** makes the use of keto ester **70** in the synthesis more effective. In addition, it also provides an unequivocal proof that diols **74** and **78** are epimeric at the chiral centre bearing the secondary hydroxyl group.

After the enone system of the keto ester **65** was successfully removed and the angular ester reduced to the desired oxidation level, our synthetic plan (Scheme 4) called for the modification of the benzyl ether moiety to an aldehyde group, in order to facilitate the incorporation of the orcinol unit. This requires two synthetic operations: the removal of the benzyl protecting group and the oxidation of the resulting alcohol.

One way of removing the benzyl protecting group involves catalytic hydrogenolysis.[60] However, our earlier experience indicated that the trisubstitued double bond is also susceptible to hydrogenation. Consequently, in spite of its simplicity, the use of catalytic hydrogenation as a means to induce the benzyl ether cleavage was not attempted. Another commonly used method for the debenzylation is by dissolving metal reduction.[72] This method is more compatible with the other existing functionalites of compound **91** and was successfully applied. Treatment of benzyl ether **91** with lithium metal in liquid ammonia at -78°C followed by gradual warm-up of the solution to room temperature and slow evaporation of excess ammonia resulted in the cleavage of the benzyl ether to give the desired alcohol **95** in 82% yield. When ammonia was replaced by ethylamine[73] and the same debenzylation was carried out at -10°C, the reduction was shown to be equally effective and the desired compound **95** was obtained in comparable yield. In the ir spectrum, a strong absorption due to hydroxyl group was observed at 3450 cm^{-1}. In the ^1H nmr spectrum, no signals due to aromatic protons were observed. The vinylic proton appeared at ∂ 5.64 as a broad singlet. Two singlets, one at ∂ 4.64 (2H) and the other at ∂ 3.38 (3H), indicated the intact methoxymethoxy unit. Three methyl singlets were observed at ∂ 1.80, 1.06 and 0.90. These data are in agreement with the structure **95** assigned to the compound. Although, in the mass spectrum, the molecular ion corresponding to the expected molecular formula was not observed, a fragment resulting from the loss of a methoxymethoxy unit was observed at m/z 219.1747. Furthermore, its molecular weight, in accord with the expected molecular formula $C_{17}H_{30}O_3$, was verified by the chemical ionization mass spectrum to be 282.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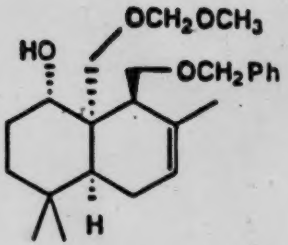
OCH₂OCH₃
OCH₂Ph
H

92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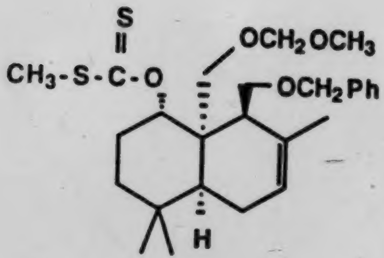
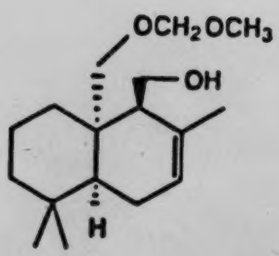
OCH₂Ph
H

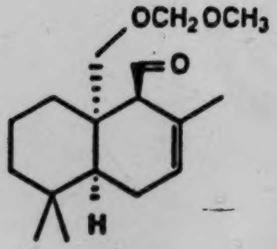
93


S
CH₃-S-C-O
OCH₂OCH₃
OCH₂Ph
H

94


OCH₂OCH₃
OH
H

95


OCH₂OCH₃
O
H

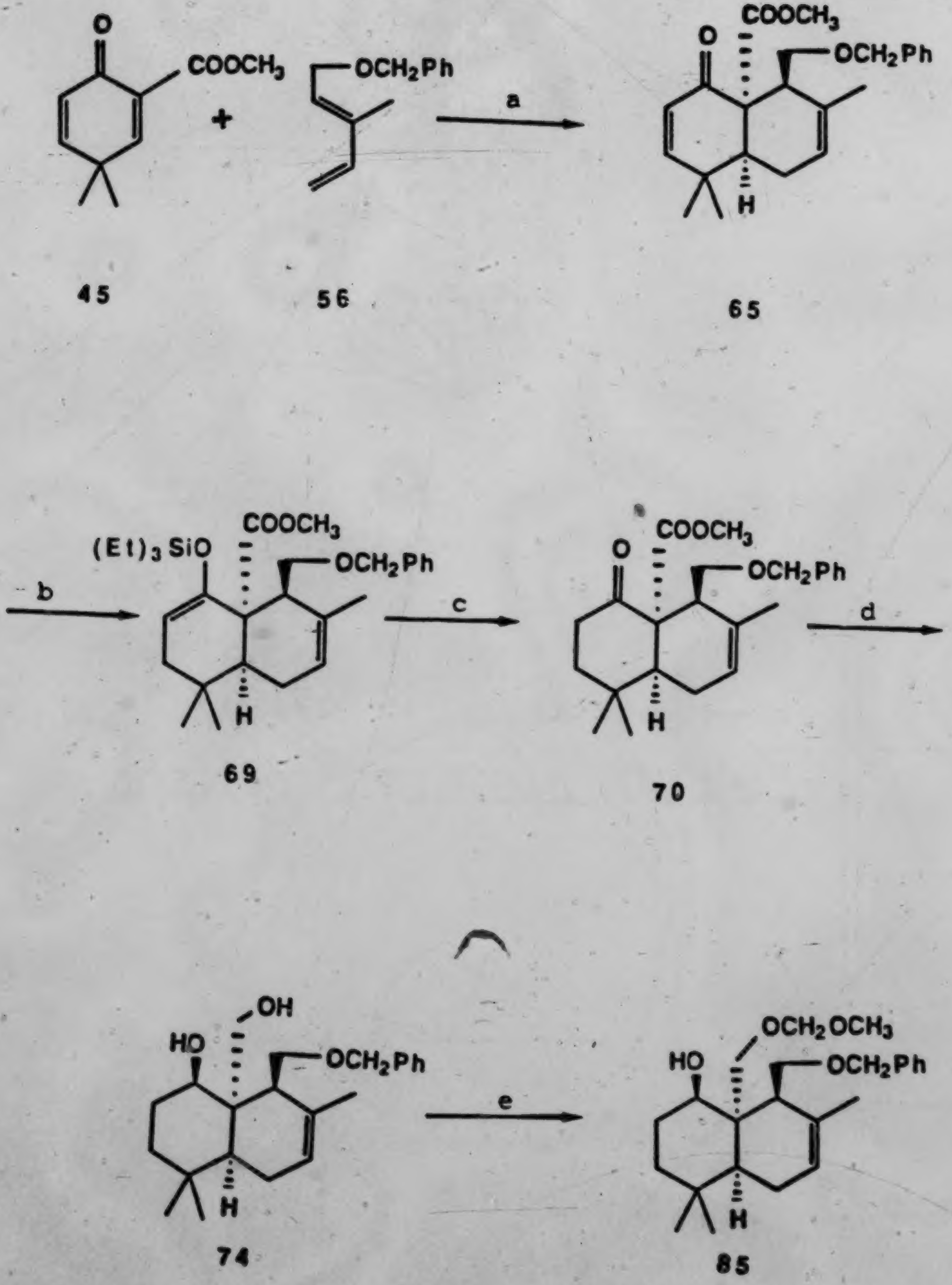
96

To oxidise the primary alcohol to the aldehyde level, compound **95** was subjected to the Swern[74] modification of Moffatt oxidation.[75] Thus, alcohol **95** was added slowly to a mixture of oxalyl chloride and dimethyl sulfoxide in dichloromethane at -60°C. The solution was allowed to warm up to -10°C and triethylamine was added. A single product was isolated in 75% yield. It was shown by the following spectral data to possess the desired structure of **96**. The mass spectrum of the compound suggested the molecular formula to be $C_{17}H_{28}O_3$ with a molecular ion peak at 280.2038. In the ir spectrum, the compound showed the absence of any hydroxyl absorptions. A strong absorption at 1660 cm^{-1} suggested the presence of a carbonyl group. Although normally only α,β-unsaturated carbonyls absorb in this region, the presence of a conjugated system was ruled out by the ^1H nmr spectrum of the compound which showed a doublet with a coupling constant 4 Hz at ∂ 9.78 readily attributed to the aldehyde proton. The ^1H nmr spectrum also showed a broad singlet at ∂ 5.60 for the vinylic proton. This observation is in agreement only with the presence of the β,γ- unsaturated aldehyde as depicted in structure **96**.

Aldehyde **96** could also be effectively prepared by the oxidation of alcohol **95** with pyridinium chlorochromate.[62] Treatment of alcohol **95** with three equivalents of pyridinium chlorochromate in dichloromethane at room temperature for 3 hours followed by filtration through magnesium sulfate gave the aldehyde **96** in 80% yield. The simplicity of this procedure coupled with the improved yield of the product makes it a more attractive method for the preparation of compound **96**.

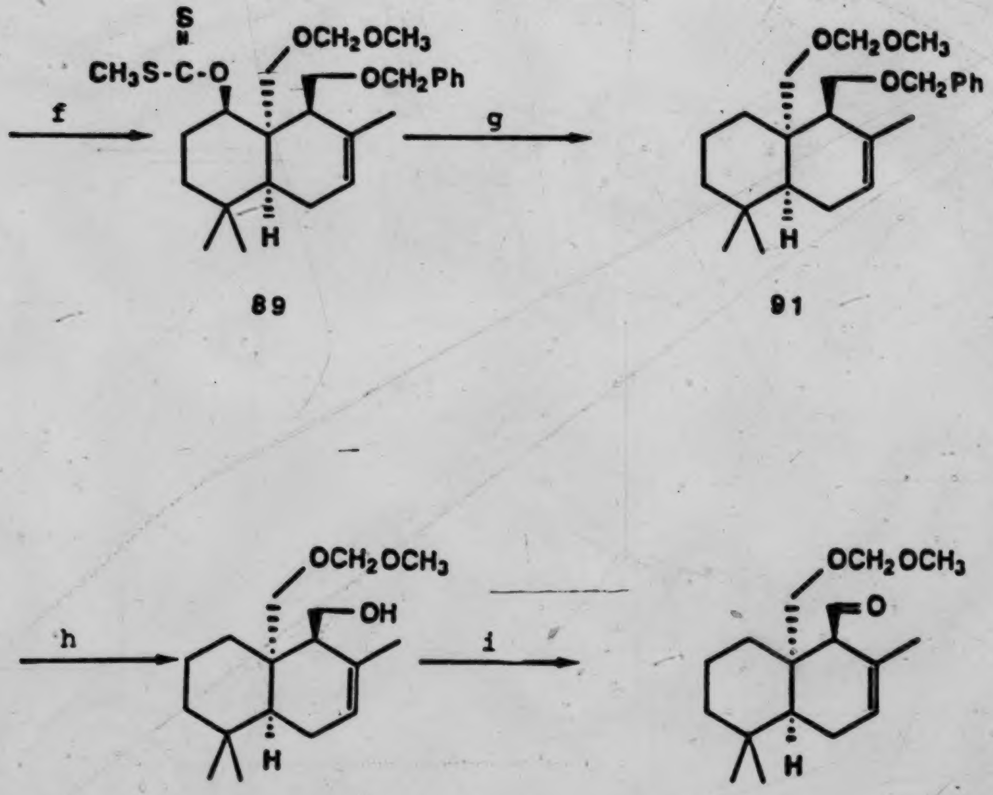
At this point, the construction of the complete sesquiterpene unit of the target molecule **1** has been successfully accomplished in nine steps from the keto ester **45** as summarized in Scheme 8. Diels-Alder reaction of **45** with diene **56** under ferric chloride catalysis gave the adduct **65**. Hydrosilylation of **65** with Wilkinson's catalyst and triethylsilane followed by cleavage of the resulting silyl enol ether **69** with tetra-*n*-butylammonium fluoride afforded the keto ester **70**. This compound was subjected to reduction with Red-Al and the diols **74** and **78** obtained were individually transformed to the bisether **91** via selective ether formation using chloromethyl methyl ether and potassium hydride. This was followed by xanthate formation with sodium hydride, carbon disulfide and methyl iodide. Compounds **89** and **94** thus formed were subsequently individually reduced to give the same hydrocarbon **91**. Debenzylation of **91** was effected by lithium in liquid ammonia or ethylamine and the alcohol obtained was oxidized by pyridinium chlorochromate or under Swern's oxidation conditions to give aldehyde **96**.

In order to facilitate the introduction of the required orcinol moiety, the dimethyl ether of orcinol (**97**) was prepared. Treatment of the sodium salt of orcinol with dimethyl sulfate in aqueous methanol[76] gave rise to an 85% yield of the corresponding dimethyl ether **98**, which showed


COOCH3
OCH2Ph
a
45
56
65
b
(Et)3SiO
c
d
69
70
OH
HO
OCH2OCH3
e
H
74
85

Scheme 8

Scheme 8 (contd)



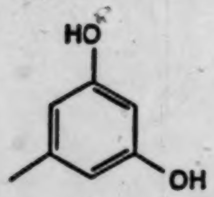
89 91 95 96

a) $FeCl_3$, Et_2O, -20°C; b) Et_3SiH, Wilkinson's catalyst, benzene, R.T; c) *n*-(Bu)4N^+F^-, THF; d) Red-Al, Et_2O; e) MOMCl, NaH, DME, -10°C; f) NaH, CS_2, MeI, DME; g) *n*-$(Bu)_3SnH$, AIBN, Toluene, reflux; h) li/ liq.NH3, t-BuOH, Et_2O, -78°C; i) PCC, CH_2Cl_2.

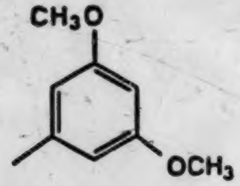
a molecular ion peak at 152.2216 for the required molecular formula $C_9H_{12}O_2$. The ^1H nmr spectrum showed, interestingly, three singlets at ∂ 6.32, 3.76 and 2.20 in a 1:2:1 ratio.The lithium salt (**99**) of orcinol dimethyl ether was readily generated at room temperature in ethereal solution by treating **98** with *n*-butyllithium. Aldehyde **96** was added to a three fold excess of the reagent **99** at 0°C and the reaction mixture was allowed to warm up slowly to room temperature. After 1 hour, by thin layer chromatographic analysis, it appeared that no reaction occurred. In an attempt to recover the starting material however, a new compound was isolated. This compound was easily characterised as the double bond isomer **100**, in which the double bond is in conjugation with the carbonyl. Its isomeric nature with the starting aldehyde **96** was clearly indicated by the mass spectrum, showing a molecular ion peak at 280.1666. The ir spectrum showed a carbonyl absorption band at 1660 cm^{-1}, while the ^1H nmr spectrum showed the absence of any vinylic protons. Furthermore, the aldehydic proton as well as the vinylic methyl group appeared at a much lower field at ∂ 10.20 and 1.96 when compared with those of the starting material, the former as a sharp singlet and the latter as a broad one.

The isolation of compound **100** instead of the expected addition product indicated that the lithium reagent **99** acted as a base rather than a nucleophile to give an incipient enolate ion **101** which could not react further with the reagent. In order to circumvent this problem, the reaction was attempted at a much lower temperature of -78°C. In this case, aldehyde **100** was again obtained as the sole reaction product.

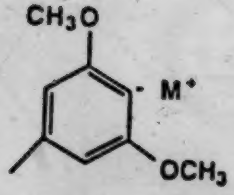
To reduce the basicity of **99**, it was decided to use the corresponding magnesium salt **102** as the nucleophile. It could be prepared by a metal exchange[77] between **99** and magnesium bromide etherate[78] as follows; Orcinol dimethyl ether **98** was treated with *n*-butyllithium at room temperature for 2 hours followed by the addition of magnesium bromide etherate. Treatment of the aldehyde **96** with the magnesium reagent **102** at -78°C to room temperature for 90 minutes resulted in the complete consumption of the starting material and the formation of a more polar material in 70% yield. To our delight, this product was readily identified as the desired adduct **103** on the basis of the following spectroscopic analyses. In the ir spectrum, the compound displayed an absorption band at 3540 cm^{-1} due to hydroxyl group and the absence of any carbonyl absorptions. In the ^1H nmr spectrum, the presence of singlets at ∂ 6.36 (2H), 3.80 (6H) and 2.24 (3H) suggested the successful addition of the orcinol reagent. In addition, the vinylic proton appeared at ∂ 6.36 as a broad singlet. Although the molecular ion corresponding to the expected molecular formula was not observed in the mass spectrum, a fragment resulting from the loss of a methoxymethoxy unit was displayed at m/z 370.2506. The presence of only a single set of signals in the ^1H nmr spectrum indicated that the coupling product was formed as



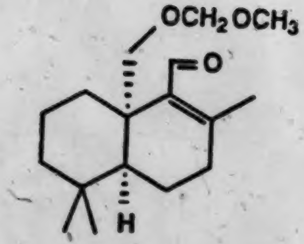
97



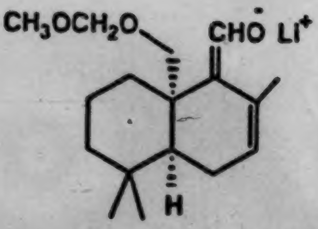
98



99 M = Li
102 M = MgBr



100



101

a single stereoisomer. Its stereochemistry at the newly generated chiral centre remains, however, to be determined.

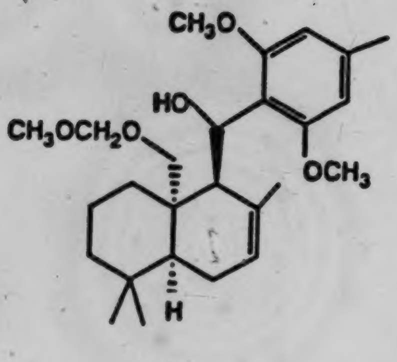
The transformation of compound **103** to siccanin (**1**) requires consecutive closures of two ether rings C and E. Obviously, the cyclisation to form the E ring first would require minimum manipulation of the existing functionalities. Indeed, the formation of E ring could be brought into effect with ease. When alcohol **103** was subjected to treatment with pyridinium *p*-toluenesulfonate[79] in dichloromethane at reflux temperature, the cyclised product **104** was formed in 68% yield. Further experiments showed that the cyclisation could be improved to a large extent using pyridinium chloride[80] in dichloromethane at reflux. Under these conditions, a quantitative yield of compound **104** was realised. In the ^1H nmr spectrum of **104** a singlet at ∂ 6.30 was attributed to the aromatic protons. The vinylic proton appeared as a broad singlet at ∂ 5.18. A doublet ($J = 8$ Hz) at ∂ 4.22 and a doublet of doublets ($J = 8$, $J' = 2$ Hz) at ∂ 3.66 were attributed to the methylene protons adjacent to the oxygen atom. The ir spectrum showed no hydroxyl group absorptions. Additional support for the assigned structure was provided by the mass spectrum, which displayed a molecular ion at 370.2510 in accord with the molecular formula $C_{24}H_{34}O_3$. Although the above spectral data indicated clearly the gross structure of the cyclisation product, the stereochemistry of its benzylic carbon could not be established. Consequently, this compound was subjected to a single crystal X-ray analysis and it was shown later to be the thermodynamically more stable epimer **104** (*vide infra*).

Prior to the X-ray analysis, compound **104** was subjected to treatment with a number of Lewis acids, including boron trifluoride and stannic chloride, in attempts to induce the ring C formation. Under a variety of conditions however, the compound was found to be stable and did not undergo the desired ring closure. This was most likely due to the low nucleophilicity of the anisole oxygen atom. To enhance its reactivity, compound **104** was subjected to demethylation. Treatment of **102** with potassium ethanethiolate, generated *in situ* from ethanethiol and potassium hydride, in *N,N*-dimethylformamide at 125°C[81,82] gave the corresponding phenol **105** in 67% yield. In order to improve the yield of phenol **105**, the following experiment was carried out. Compound **104** was treated with excess sodium cyanide in dimethyl sulfoxide at 180°C[81,83] for 8 hours. Under these conditions however, neither the starting material **104** nor the expected product **105** could be isolated from an unidentifiable complex mixture produced.

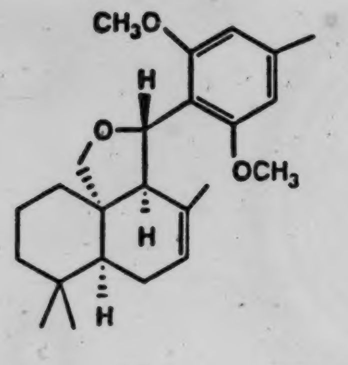
Compound **105** displayed, in the ir spectrum, an absorption at 3360 cm^{-1} suggesting the presence of a hydroxyl group. The ^1H nmr spectrum exhibited a hydroxyl signal at ∂ 7.80 which disappeared on treatment with deuterium oxide. Two additional sharp singlets in the lowfield region at ∂ 6.38 and 6.22 were attributed to the aromatic protons and a broad singlet at ∂ 5.28 was due to the vinylic proton. Five other singlets, each integrating to three protons, were also observed respectively at ∂ 3.74, 2.38, 1.56, 0.92 and 0.84. Additional support for the assigned structure was obtained from the mass spectrum of the compound, which displayed an ion peak at m/z 355.2236 for the fragment resulting from the loss of a proton, a process which is charecteristic of phenolic compounds.

In order to induce the ring C formation phenol **105** was subjected to treatment with a number of acids. With protic acids such as pyridinium chloride[80] in dichloromethane, camphorsulfonic acid in tetrahydrofuran, and aqueous hydrochloric acid in tetrahydrofuran, no reaction was observed and the starting material was recovered intact. With boron trifluoride etherate in dichloromethane at 0°C, a pink colour developed immediately, which disappeared after five minutes while the solution was slowly warmed to room temperature. After 30 minutes, two products were isolated in ca. 1:1 ratio. These compounds were readily separated by flash column chromatography on silica gel.

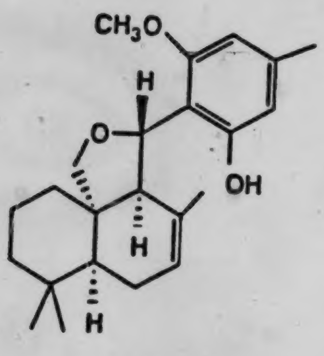
The faster moving compound, isolated in 61% yield, showed no characteristic absorptions of either hydroxyl or carbonyl groups in the ir spectrum. In the ^{1}H nmr spectrum, two vinylic protons, each appearing as a broad singlet, were observed at ∂ 6.28 and 5.26. Two doublets (J = 10 Hz each) were found at ∂ 4.52 and 3.80. These signals could be attributed to methylene protons adjacent to an oxygen atom. In addition, a vinylic methyl group appeared at ∂ 1.76 as



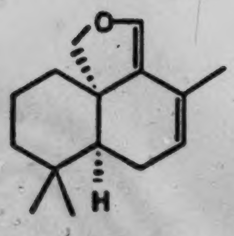
103



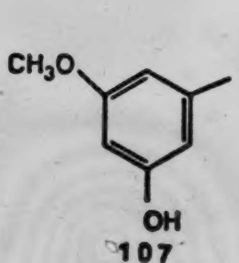
104



105



106



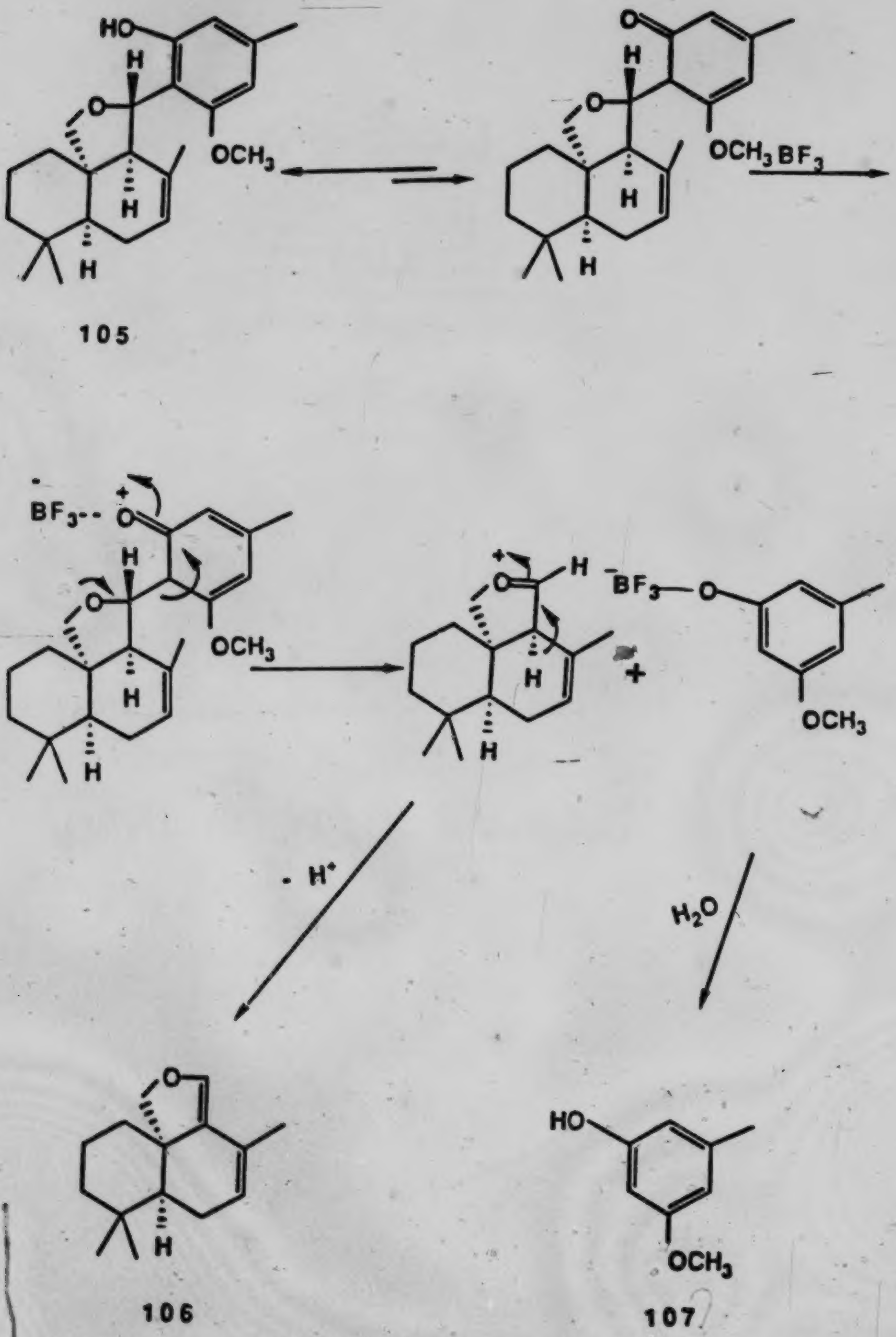
107

a singlet. These ^{1}H nmr spectral data coupled with the complete absence of signals due to aromatic protons suggested structure **106** for this compound. The assignment was further confirmed by the mass spectrum which showed a molecular ion peak at 218.1668 for the required molecular formula $C_{15}H_{22}O$.

The slower moving product, isolated in 70% yield, was readily identified as the orcinol monomethyl ether **107**. Its mass spectrum displayed a molecular ion at 138.0680 for the molecular formula $C_8H_{10}O_2$. The ^{1}H nmr spectrum showed three singlets at ∂ 6.20, 6.12 and 6.10, a methoxy singlet at ∂ 3.74 and a methyl singlet at ∂ 2.42.

Compounds **106** and **107** were also obtained when phenol **105** was subjected to treatment with stannic chloride in benzene at room temperature for 30 minutes. The degradation of phenol **105** to give compounds **106** and **107** could be rationalized by invoking an acid catalysed retro-Aldol type reaction on the keto form of the starting compound as outlined in Scheme 9.

Iodolactonisation[43,84] is a well established process for the conversion of unsaturated acids to cyclic lactones. This process of cyclisation has been extended to other unsaturated compounds containing substituents such as hydroxyl group that can act as an internal nucleophile.[84] This method was attempted and the phenolic compound **105** was treated with potassium carbonate and iodine in methanol. However, no detectable amount of the cyclised product was


HO
H
O
OCH3
H
H
105
O
H
O
OCH3 BF3
H
H
BF3-- O
H
O
OCH3
H
H
O
H
BF3—O
H
H
+
OCH3
- H+
H2O
O
H
106
HO
OCH3
107

Scheme 9

observed even after 6 hours of reflux. The use of a stronger base such as sodium hydroxide also proved to be ineffective.

Analogous to iodolactonisation, a cyclofunctionalisation technique to obtain cyclic phenyl ethers from suitable olefinic phenols using phenylselenenyl chloride has been developed by Clive and co-workers.[85] Application of this method to compound **105** also failed to produce the desired product. When **105** was treated with 2 equivalents of phenylselenenyl chloride in ethyl acetate at room temperature for 4 hours, only the starting material was recovered. Similar results were obtained when a catalytic amount of imidazole was added to the reaction mixture.

Another well known method for the cyclisation of unsaturated carboxylic acids and alcohols to give the corresponding lactones and cyclic ethers respectively involves the use of a mercuric salt as an activating reagent.[86,87] Accordingly, phenol **105** was subjected to an intramolecular oxymercuration with mercuric acetate in methanol at room temperature for 6 hours. The expected cyclisation product **108**, without isolation, was immediately reduced by addition of sodium borohydride. To our delight the product thus obtained in 72% yield was shown to be non identical with either **106** or **107** by thin layer chromatography. Furthermore, the ir spectrum revealed the absence of any hydroxyl absorptions, strongly indicating that the cyclisation has occurred. This was also supported by the ^{1}H nmr spectrum, in which the broad singlet normally observed for the vinylic proton in this series of compounds was absent. As well, the vinylic methyl that normally appeared at around ∂ 1.6 experienced an upfield shift by roughly 0.3 ppm to ∂ 1.2. However as shown below, a comparision of the ^{1}H nmr spectrum of this compound with that reported[2] for the siccanin methyl ether (**43**) reveals that they are nonidentical.

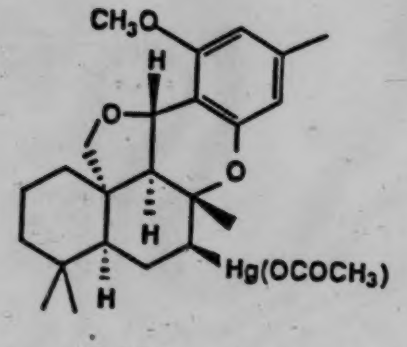
The ^{1}H nmr spectrum of siccanin methyl ether (**43**) ∂: 4.95 (d, 1H, J = 8.5 Hz, Ar-CH-), 4.02 (d, 1H, J = 8 Hz, -OC**H**H-), 3.80 (s, 3H, -OCH$_3$), 3.25 (d, 1H, J = 8 Hz, -OCH**H**-), 2.23 (s, 3H, Ar-CH$_3$), 1.16 (s, 3H, O-C-CH$_3$), 0.80 (s, 6H, *gem*-dimethyl)

The ^{1}H nmr spectrum of the synthetic product ∂: 6.32 and 6.24 (each s, 1H each, aromatic), 5.56 (bs, 1H, Ar-CH-O), 4.16 (d, 1H, J = 8 Hz, -C**H**H-O), 3.80 (s, 3H, -OCH$_3$), 3.56 (dd, 1H, J = 8, J' = 1 Hz, -CH**H**-O), 2.28 (s, 3H, Ar-CH$_3$), 1.50 (s, 3H, OC-CH$_3$), 0.84 and 0.82 (each s, 3H each, *gem*-dimethyl).

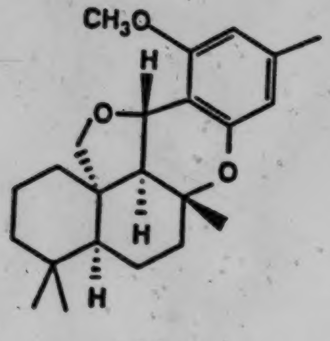
Clearly, this synthetic product must be a stereoisomer of the one derived from the natural product. Since three asymmetric centres have been previously established unequivocally by X-ray studies on diol **74** (*vide supra*), it is logical to assign structure **109** to the synthetic compound which we named as iso-siccanin methyl ether. At this point, the results of the X-ray analysis on compound **104** became available. As shown in Figure 2, which depicts the three dimensional structure of the compound, the benzylic methine proton is indeed *trans* to the neighbouring hydrogen atom. Cyclisation of its derivative **105** is expected to lead to compound **109** with a *trans* fused C/E ring junction and not siccanin methyl ether (**43**) in which the C/E ring junction is *cis*-fused.

Up to this point, it has been demonstrated that the complete carbon skeleton of the target molecule can be assembled rather effectively by an intermolecular Diels-Alder approach. The sesquiterpene unit was installed in a total of nine synthetic steps (Scheme 8) from dienone ester **45** with complete control of the correct stereochemistry. The orcinol moiety was subsquently introduced by a Grignard reaction. This was followed by two consecutive ether formation processes involving a total of three synthetic steps as shown in Scheme 10. However, in order to apply this approach successfully to the synthesis of the natural product, it is necessary to modify the synthesis in such a way that the stereochemistry of the two interrelated asymmetric centres can be corrected.

One simple conceivable solution to the problem is via the epimerisation of the benzylic chiral carbon present in compound **104**. The hydrogen atom being both benzylic and adjacent to an ether linkage is expected to be rather acidic. Deprotonation followed by kinetic protonation could, in principle, lead to the required stereochemistry as shown in **110**. Subsquent cyclisation is expected to give siccanin methyl ether (**43**). Thus, compound **104** was subjected



108



109

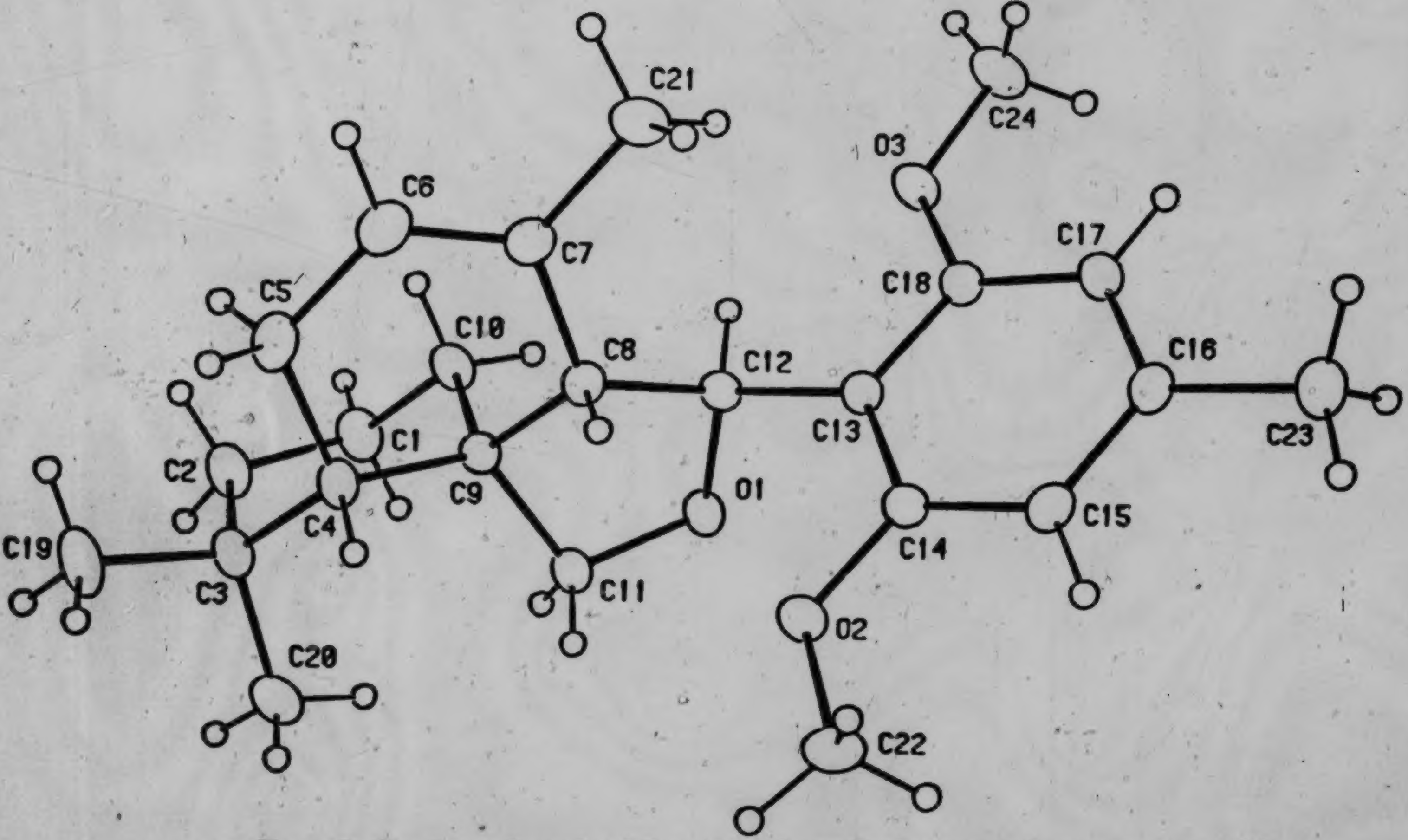
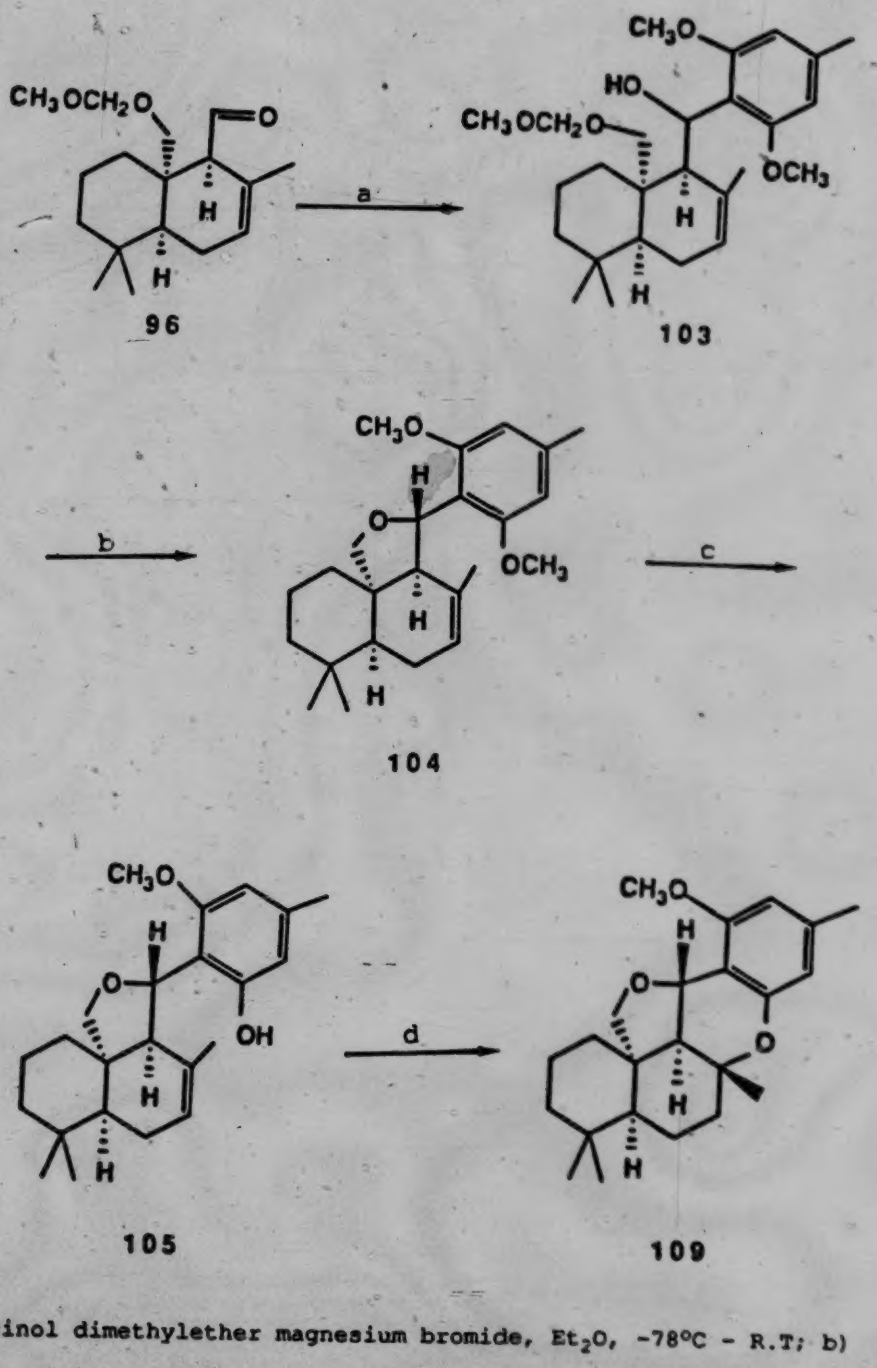


Figure 2 The three dimensional X-ray crystallographical structure of tricyclic ether **104**



a) orcinol dimethylether magnesium bromide, Et_2O, -78°C - R.T; b) Py.HCl, CH_2Cl_2, reflux; c) KH, EtSH, DMF, 115°C; d) $Hg(OAc)_2$, MeOH, $NaBH_4$.

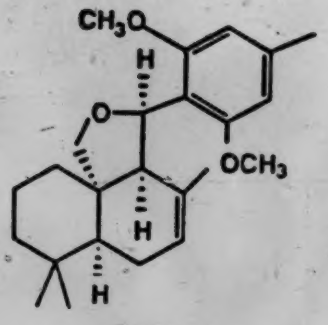
Scheme 10

to treatment with an excess of *n*-butyllithium in ether using various temperatures ranging from -78°C to room temperature. In no case however, could the desired isomer **110** be detected after the reaction was quenched with methanol. When the reactions were quenched with 99% deuterium oxide, the starting material recovered showed no deuterium incorporation by ^{1}H nmr analysis. Clearly, the desired deprotonation has not occurred under the conditions employed. Although the use of an even stronger base such as *sec*-butyllithium represents a further possiblity for the epimerisation, this remains to be studied.

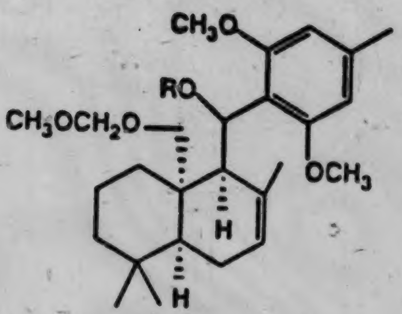
Another possiblity to correct the stereochemistry is to induce the cyclisation of C ring first from compound **103**. Cyclisation of a suitable intermediate such as **111** with an activating reagent like mercuric acetate is expected to give compound **112** as a result of the selective complexation of mercuric acetate with the double bond from the sterically less hindered face of the molecule.

The conversion of compound **103** to a compound of the type **111** requires protection of the hydroxyl group and demethylation. The hydroxyl protecting group must survive conditions necessary for the subsequent demethylation and cyclisation. With this in mind, the *t*-butyldiphenylsilyl ether of compound **103** was prepared by treatment with *t*-butyldiphenylsilyl chloride in the presence of potassium hydride in 1,2-dimethoxyethane at reflux for 3 hours.[88] Silyl ether **113** thus obtained in 90% yield showed no absorptions due to a hydroxyl group in its ir spectrum. In the ^{1}H nmr spectrum, it showed multiplets between ∂ 7.70 and 6.90 for the protons of the two newly introduced phenyl rings. The aromatic protons corresponding to the orcinol moiety were observed at ∂ 6.22 and 5.84 as singlets. The benzylic proton was observed as a doublet with a coupling constant of 9 Hz at ∂ 5.38. The *t*-butyl protons appeared at ∂ 0.98 as a singlet.

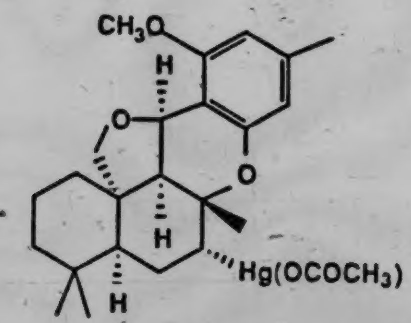
With the hydroxyl group properly protected, we turned our attention to the demethylation of one of the anisole methyl groups. Compound **113** was treated with potassium ethanethiolate in *N,N*-dimethylformamide at 125°C. Although these conditions were found previously to be highly effective for the demethylation of the compound **104**, in the present case, the desired transformation did not occur after 8 hours and the starting material was recovered with partial decomposition to give a mixture of unidentifiable compounds. These negative results could be attributed to the insufficient stability of the protecting group as well as the steric bulk of the protecting group which hinders the required demethylation. To reduce the size of the protecting group, the preparation of *t*-butyldimethylsilyl ether was attempted without success using t-butyldimethylsilyl chloride and sodium hydride in 1,2-dimethoxyethane. Alternatively, alcohol **103** was subjected to methylation with methyl iodide in the presence of potassium hydride in 1,2-dimethoxyethane at room temperature for 3 hours. The corresponding methyl ether **114** was obtained in 83% yield. The following spectral



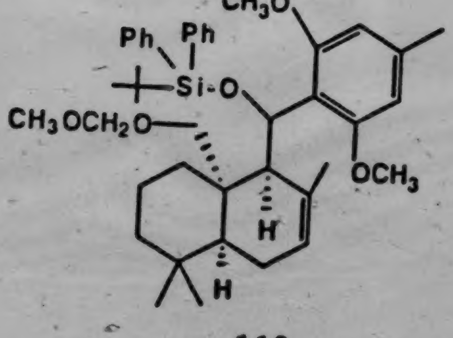
110



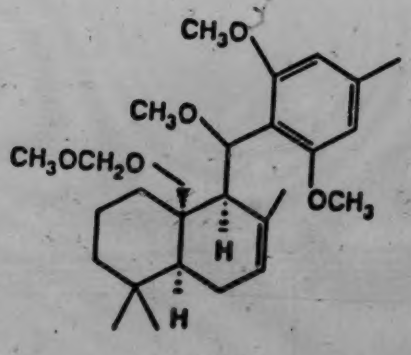
111



112



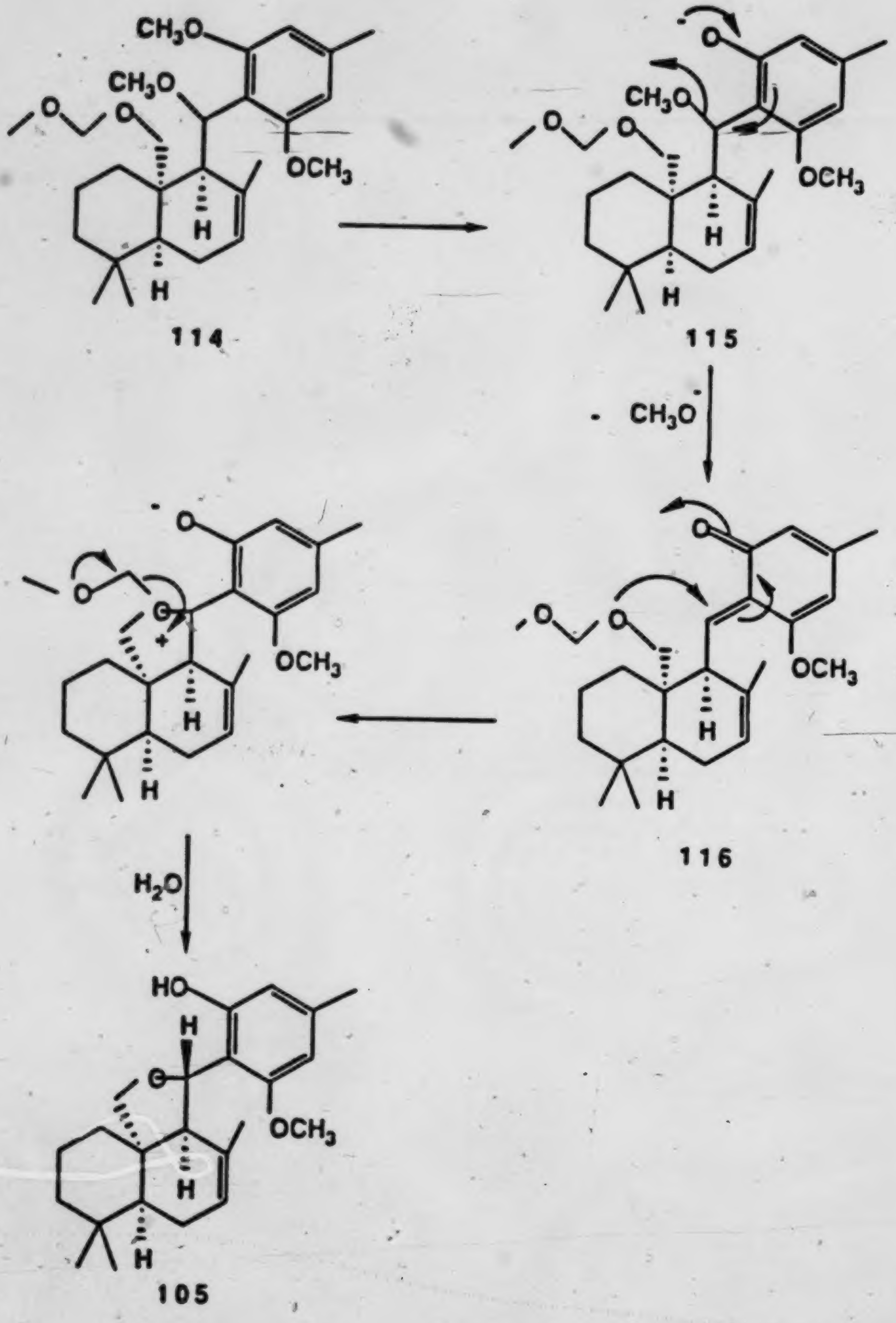
113



114

data are in agreement with the assigned structure. The compound showed no absorption due to hydroxyl group in its ir spectrum. In the ^{1}H nmr spectrum, the aromatic protons were observed at ∂ 6.38 as a singlet. The benzylic proton appeared at ∂ 4.90 as a doublet with a coupling constant of 10 Hz. The methylene protons between two oxygen atoms appeared as a singlet at ∂ 4.80, and the anisole methyl protons appeared at ∂ 3.80 as a singlet. Although the molecular ion peak corresponding to the expected molecular formula was not observed in the mass spectrum of the compound, a fragment resulting from the loss of a methanol unit was observed at m/z 370.3508.

With the hydroxyl group of compound **103** properly protected, the demethylation was attempted. Accordingly, ether **114** was treated with potassium ethanethiolate in *N,N*-dimethylformamide at 125°C for 8 hours. The reaction proceeded cleanly and a product was formed in good yield (60%). Surprisingly, this compound showed the absence of methoxymethyl group and the benzylic methoxy group in the ^{1}H nmr spectrum. A comparison of its spectral data with those previously obtained for phenol **105** revealed that it is identical with phenol **105**. A mechanistic rationale for the formation of this compound is outlined in Scheme 11. After the initial demethylation, the resulting phenoxide **115** could, in principle, eliminate the benzylic methoxy group to give the intermediate **116**. Michael addition followed by

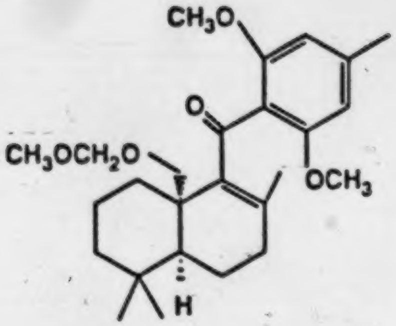

CH3O
CH3O
OCH3
H
H
114
O
CH3O
OCH3
H
H
115
- CH3O⁻
O
OCH3
H
H
116
O
O
+
OCH3
H
H
H2O
HO
H
O
OCH3
H
H
105

Scheme 11

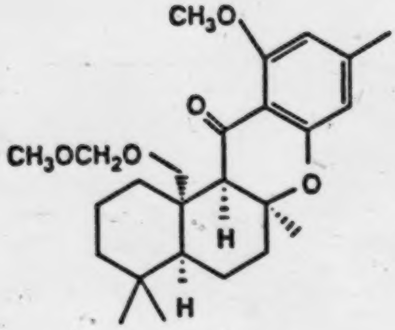
the elimination of a methoxymethyl unit could then lead to the formation of the observed product **105**.

An alternative process for the formation of ring C is to oxidise the benzylic hydroxyl group to a ketone, with concomitant migration of the carbon-carbon double bond into conjugation with the ketone thus formed (**103** → **117**). Demethylation followed by Micheal addition could, in principle, give ketone **118**. Towards this end, alcohol **103** was subjected to oxidation with pyridinium chlorochromate, buffered with sodium acetate, in dichloromethane at room temperature for 3 hours. Apparently, these oxidation conditions were too severe. Neither the starting material nor the desired product was isolated. Instead, a complex mixture containing a number of unidentifiable compounds was formed. Consequently, alcohol **103** was subjected to Swern oxidation by treatment with a mixture of oxalyl chloride and dimethyl sulfoxide at -60°C, followed by gradual warm-up to -10°C and addition of triethylamine. Under these conditions, a major product was formed in 52% yield. To our disappointment, this compound was identified as ether **104** by comparison of the spectral data. Presumably, due to the ease of cyclisation to form ring E, the substrate took this course of reaction; the expected intermediate **119** underwent a substitution reaction with the neighbouring ether oxygen instead of the desired oxidation as shown Scheme 12.

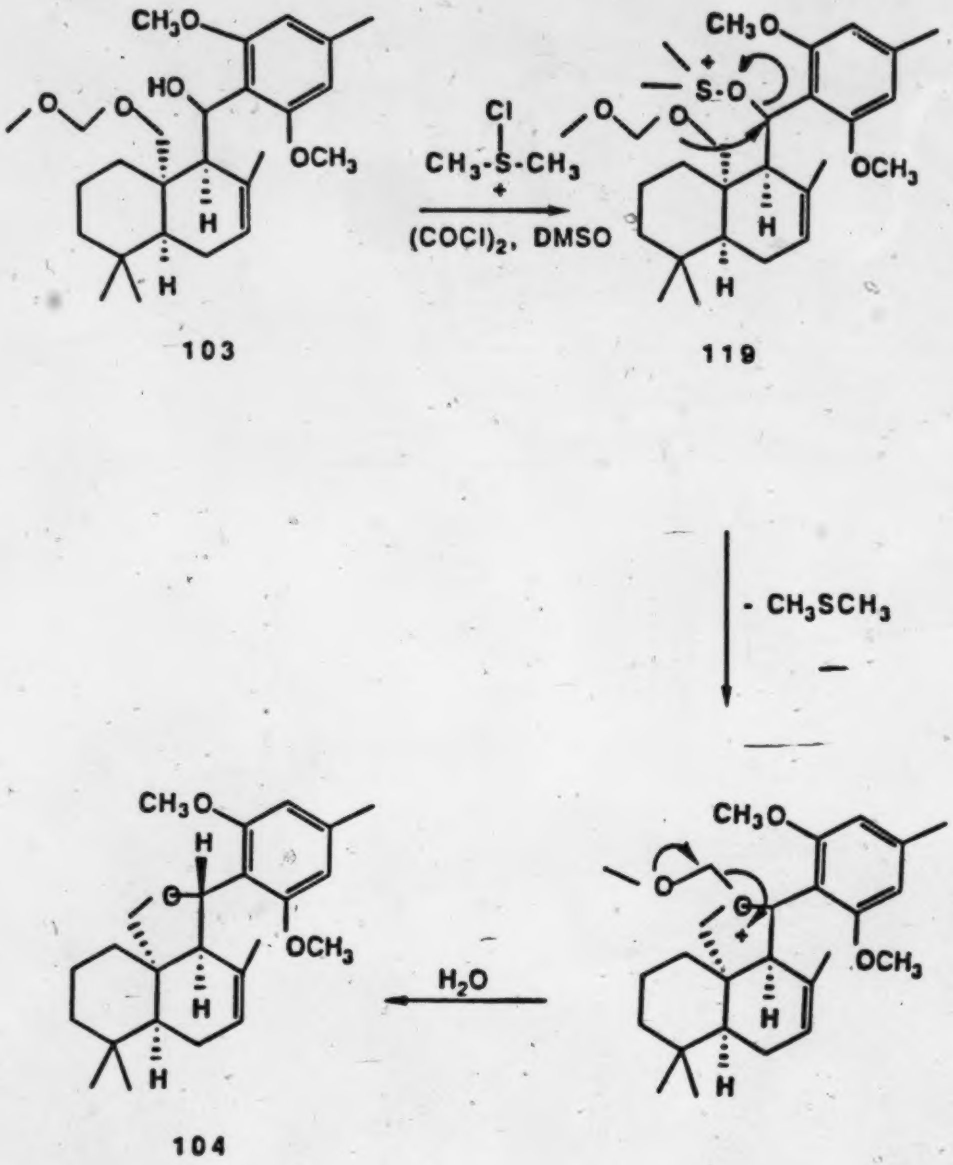
To inhibit the undesired E ring formation, an excellent possibility exists, which involves the formation



117



118

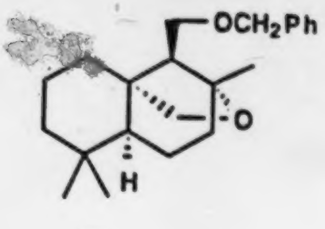

CH₃O
HO
OCH₃
H
H
103
Cl
CH₃-S-CH₃
+
(COCl)₂, DMSO
CH₃O
S-O
+
OCH₃
H
H
119
- CH₃SCH₃
CH₃O
OCH₃
H
H
H₂O
CH₃O
H
O
OCH₃
H
H
104

Scheme 12

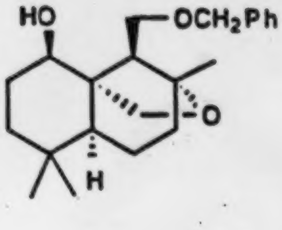
of a bridged system as shown in compound **120**. The bridged ether would serve for two purposes. The E ring formation is now sterically forbidden. In addition, it serves also to protect the hydroxyl group.

The most direct route leading to compound **120** would involve cyclisation of diol **74** to give **121** followed by the removal of the secondary hydroxyl group. Treatment of diol **74** with aqueous hydrochloric acid in refluxing tetrahydrofuran gave, in 60%, yield a hydroxy ether which showed a hydroxyl absorption band at 3510 cm^{-1} in the ir spectrum. In the mass spectrum, a molecular ion peak at 344.2353 was in accord with the expected molecular formula $C_{22}H_{32}O_3$. These spectral data were in agreement with the desired reaction product **121**. However, in the ^1H nmr spectrum, a doublet of doublets at ∂ 3.32 (J = 8, J' = 6 Hz) could be readily attributed to a hydroxyl proton, since it disappeared on addition of deuteurium oxide. The coupling pattern of this signal suggested the presence of an hydroxymethylene unit. Based on this evidence, the structure **122** was assigned to the compound.

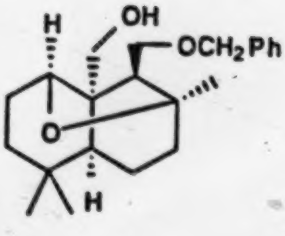
In further confirmation of the structure, compound **122** was converted to the corresponding xanthate **123** by treatment with excess sodium hydride, carbon disulfide and methyl iodide in 1,2-dimethoxyethane for 5 hours. The xanthate thus obtained in 58% yield showed a thiocarbonyl absorption at 1240 cm^{-1} in the ir spectrum. A molecular ion peak at 434.1947 was displayed in the mass spectrum in accord



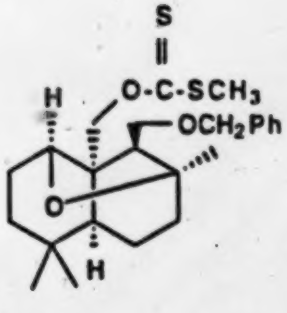
120



121



122



123

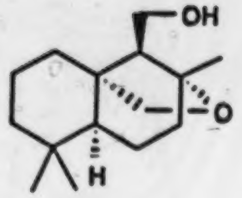
with the expected molecular formula $C_{24}H_{34}S_2O_3$. The ^1H nmr spectrum clearly indicated that the xanthate moiety was linked to a methylene carbon. Two mutually coupled doublets (J = 12 Hz) characteristic of a methylene group attached to a xanthate moiety appeared at ∂ 4.82 and 4.56.

As a consequence of the above observations an alternative route leading to the cyclic ether **120** was investigated. Diether **91** was selectively hydrolysed and cyclised with aqueous hydrochloric acid in refluxing tetrahydrofuran to give the desired cyclic ether **120** in 53% yield. The ir spectrum of the compound showed absorption at 1073 cm^{-1} for the five-membered cyclic ether. A molecular ion peak at 328.2399 in the mass spectrum suggested a molecular formula of $C_{22}H_{32}O_2$. In the ^1H nmr spectrum, the aromatic protons were observed as a multiplet at ∂ 7.40, while the benzylic protons appeared as two doublets at ∂ 4.78 and 4.72, each with a coupling constant of 12 Hz. The methylene protons adjacent to the oxygen atom appeared as a singlet at ∂ 3.54. The three singlets at ∂ 1.34, 0.96 and 0.84 were assigned to the methyl groups.

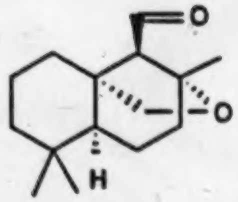
The cleavage of the benzyl ether linkage present in compound **120** was effected by dissolving metal reduction. On treatment with excess of lithium metal in liquid ammonia for 2 hours, the compound was converted to the corresponding alcohol **124** in 83% yield. The compound showed a characteristic hydroxyl absorption in the ir spectrum at 3400 cm^{-1}. The ^1H nmr spectrum displayed a complex multiplet between ∂ 3.70 and 3.40 for the four methylene protons adjacent to the oxygen atoms. Furthermore, signals due to aromatic protons were not observed. The mass spectrum of the compound confirmed the molecular formula to be $C_{15}H_{26}O_2$ with a molecular ion peak at 238.1938.

Oxidation of the alcohol **124** with pyridinium chlorochromate in dichloromethane at room temperature for 2 hours resulted in the formation of the desired aldehyde **125** in 81% yield. A molecular ion peak at 236.1782 in the mass spectrum confirmed the required molecular formula $C_{15}H_{24}O_2$. In the ^1H nmr spectrum, a doublet with a coupling constant of 4 Hz at ∂ 10.78 was assigned to the aldehydic proton. The methylene protons adjacent to the oxygen atom were observed as a singlet at ∂ 3.74. Three more singlets werw obsereved at ∂ 1.30, 0.96 and 0.74 for the methyl groups.

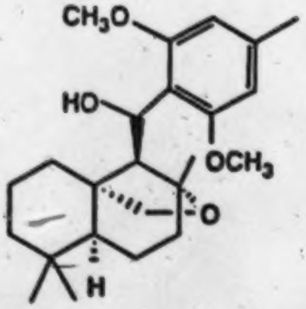
Addition of aldehyde **125** to a solution of the lithium reagent **99** in ether at room temperature resulted in the formation of the adduct **126**. The compound obtained in 90% yield showed, in the ir spectrum, an absorption due to a hydroxyl group at 3400 cm^{-1} and no carbonyl absorptions. In the ^1H nmr spectrum, the presence of singlets at ∂ 6.46 (2H), 3.76 (6H) and 2.30 (3H) indicated the incorporation of the orcinol moiety into the compound. Although the molecular ion corresponding to the expected molecular formula was not observed in the mass spectrum, a fragment resulting from the loss of a water molecule was observed at m/z 370.2506. The presence of only one set of signals in the ^1H nmr



124



125



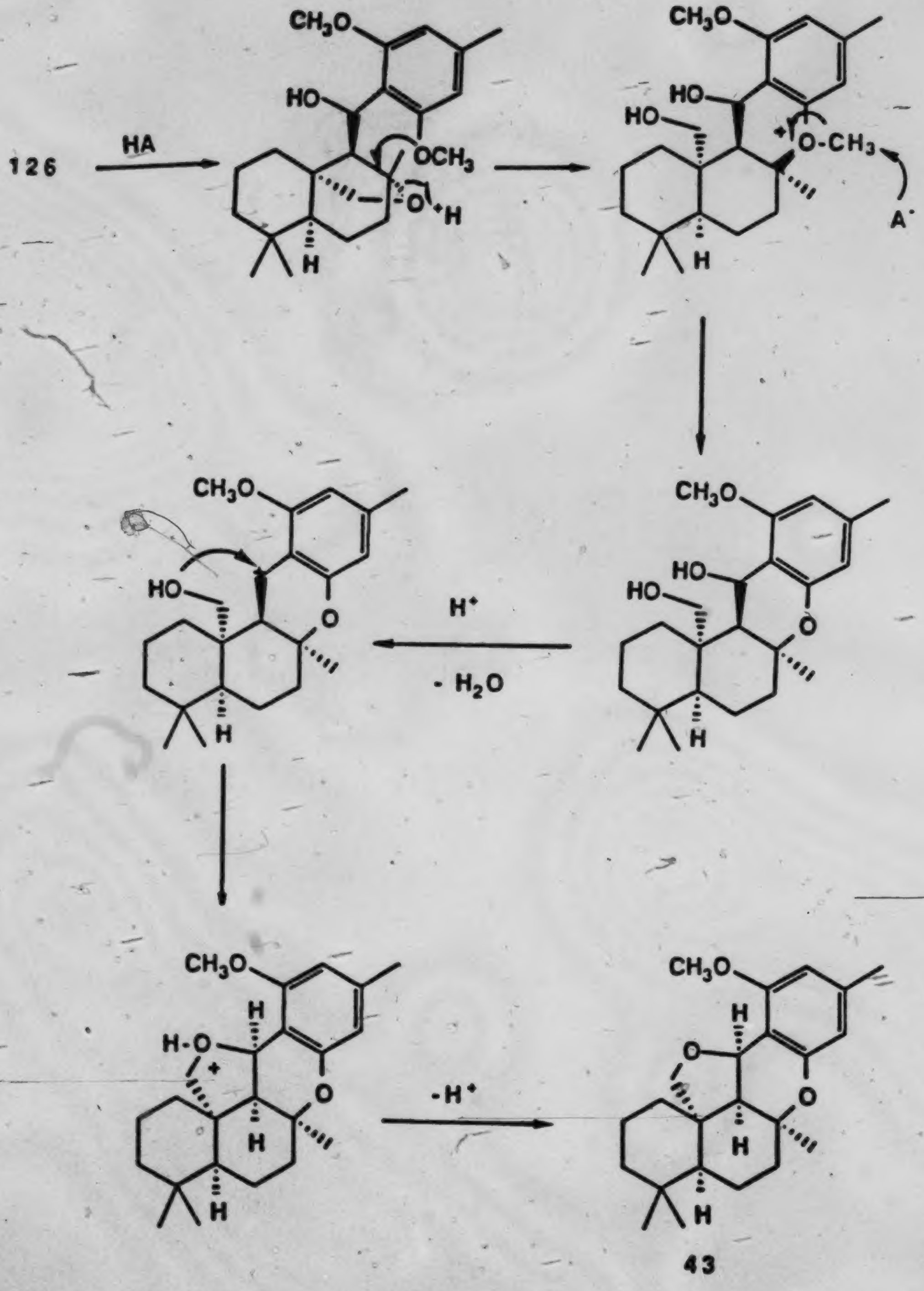
126

spectrum suggested that the coupling product was formed as a single stereoisomer. Its stereochemistry at the newly generated chiral centre remains, however, to be determined.

As shown in Scheme 13, alcohol **126** could, in principle, undergo consecutive cyclisations to provide siccanin methyl ether (**43**) under acid catalysis. However, the compound was found to be stable to 1 N aqueous hydrochloric acid in refluxing tetrahydrofuran and to boron tribromide in dichloromethane at room temperature.[89] In both cases, the starting material was recovered intact. At the present time, we are studying the demethylation of compound **126** in order to enhance its reactivity towards the formation of ether rings C and E.

Studies are also currently being undertaken on an approach, which is also designed to induce the C ring formation prior to the formation of ring E. This approach employs, as the starting material, acetal **84** which was readily avialable as a by-product from the reaction of diol **74** with chloromethyl methyl ether and sodium hydride (*vide supra*).

Debenzylation of the acetal **84** with lithium metal in liquid ammonia gave alcohol **127** in 58% yield. The compound showed, in the ir spectrum, an absorption band at 3400 cm^{-1} due to hydroxy group. In the ^1H nmr spectrum, no signals were observed for the aromatic protons. A broad singlet at ∂ 5.40 was attributed to the vinylic proton. Two doublets, each with a coupling constant of 8 Hz, appeared at ∂ 5.20 and 4.84



Scheme 13

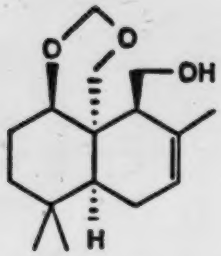
due to the methylene protons adjacent to two oxygen atoms. In addition, three singlets for the methyl groups were observed at ∂ 1.80, 0.94 and 0.82. Although in the mass spectrum, a molecular ion peak due to the expected molecular formula was not observed, a fragment resulting from the loss of a water molecule appeared at m/z 248.1788.

Oxidation of the alcohol **127** with pyridinium chlorochromate in dichloromethane for 3 hours gave the corresponding aldehyde **128** in 80% yield. The mass spectrum of the compound suggested the molecular formula $C_{16}H_{24}O_3$ with a molecular ion at 264.1720. In the ir spectrum, the compound showed the absence of any hydroxyl absorptions. An intense band at 1711 cm^{-1} suggested the presence of a carbonyl group. In the ^1H nmr spectrum of the compound, a doublet with a coupling constant of 2 Hz was observed at ∂ 10.16. This signal was readily attributed to the aldehydic proton. The vinylic proton was observed as a broad singlet at ∂ 5.50, whereas the methylene protons adjacent to two oxygen atoms appeared as a pair of doublets, each with a coupling constant of 6 Hz, at ∂ 5.24 and 4.92.

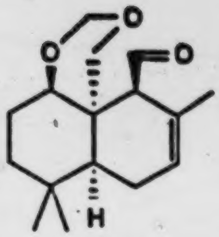
When aldehyde **128** was subjected to treatment with the magnesium reagent **102** derived from orcinol dimethyl ether **98**, a mixture of two epimeric alcohols **129** was formed. The major alcohol, which was obtained in 59% yield, showed a hydroxyl absorption at 3320 cm^{-1} in the ir spectrum. In the ^1H nmr spectrum, the singlets at ∂ 6.28 (2H), 3.76 (3H) and 2.30 (3H) were attributed to the orcinol moiety. The vinylic proton appeared at ∂ 5.50 as a broad singlet and the methylene protons adjacent to two oxygen atoms were displayed as doublets at ∂ 5.12 and 4.80, each with a coupling constant of 7 Hz.

The minor product obtained in 23% yield displayed, in the ir spectrum, a strong absorption at 3520 cm^{-1} characteristic of hydroxy group. The ^1H nmr spectrum showed singlets at ∂ 6.14 (2H), 3.80 (6H) and 2.30 (3H) due to the orcinol moiety. A broad singlet at ∂ 5.66 was due to the vinylic proton and two doublets (J = 7 Hz each) observed at ∂ 5.18 and 4.92 were attributed to the methylene protons adjacent to two oxygen atoms. Although the molecular ion corresponding to the expected molecular formula was not observed in the mass spectrum, a fragment resulting from the loss of a water molecule was displayed at m/z 398.2467.

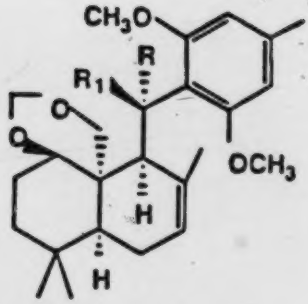
The conversion of the minor alcohol **129** to the corresponding phenol **130** was easily carried out with potassium ethanethiolate in *N,N*-dimethylformamide at 125°C. The phenol **130** obtained in 80% yield showed the following spectral properties in accord with the assigned structure. A strong absorption at 3440 cm^{-1} in the ir spectrum suggested the presence of a hydroxyl group. The mass spectrum displayed a fragment at m/z 401.2316 resulting from loss of a proton. In the ^1H nmr spectrum, singlets were observed at ∂ 6.48 (1H), 6.22 (1H), 3.74 (3H) and 2.30 (3H) due to the orcinol portion of the molecule. The methylene protons adjacent to two



127

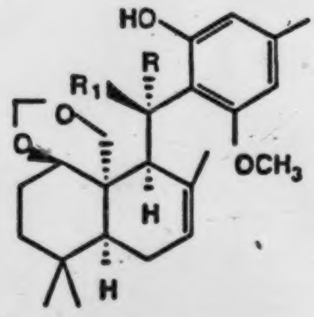


128



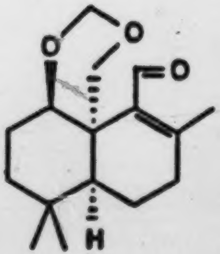
R, R_1 = H, OH

129



R, R_1 = H, OH

130



131

oxygen atoms were displayed at ∂ 5.20 and 4.82 as doublets each with a coupling constant of 6 Hz.

While the conversion of the minor alcohol **129** to the corresponding phenol **130** was rather straightforward, the attempted demethylation of the major alcohol **129** gave rise to rather unexpected results. Its treatment with potassium ethanethiolate resulted in the formation of two products, one of which was readily identified as orcinol monomethyl ether (**107**). The other was found to be aldehyde **131** which showed a strong absorption at 1667 cm^{-1} in the ir spectrum indicating the presence of a conjugated carbonyl group. In the ^1H nmr spectrum, the signals due to the orcinol moiety and the vinylic proton were absent, whereas an aldehydic proton appeared at ∂ 10.34 as a singlet. Furthermore, a methyl singlet was found in the unusually lowfield at ∂ 2.18 indicating the migration of the carbon-carbon double bond into conjugation with the carbonyl group. The molecular formula $C_{16}H_{24}O_3$ was confirmed by the mass spectrum showing a molecular ion peak at 264.1724. The formation of compounds **107** and **131** could be rationalised by invoking a mechanistic pathway similar to that outlined in Scheme 8 for the degradation of **105** to give **106** and **107**.

In conclusion, the Diels-Alder approach described in this thesis can be applied rather effectively to the construction of the carbon skeleton of siccanin (**1**) as demonstrated in the synthesis of isosiccanin methyl ether (**109**). The application of this approach to the synthesis of the naturally occurring compound requires effective control of the two inter-related asymmetric centres present in C ring. In order to achieve this, two modifications are under current investigation. One involves the use of alcohol **126** as a potential synthetic intermediate and the other proceeds via the alcohols **129**.

EXPERIMENTAL

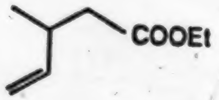
General

Melting points were recorded on a Kofler hot stage apparatus and are uncorrected. Elemental analyses were performed by the microanalytical laboratory of this department. Infrared (ir) spectra were recorded on a Perkin-Elmer model 457 or Nicolet 7-199 FT-IR spectrophotometer. Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on a Bruker WP-80, Bruker WH-200 or Bruker WH-400 spectrometer and were obtained on solutions in deuterochloroform with tetramethylsilane as internal standard. Carbon-13 nuclear magnetic resonance spectra (^{13}C nmr) were recorded on a Bruker WH-200 or Bruker WH-400 spectrometer and were recorded on solutions in deuterochloroform. The following abbreviations are used: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra (ms) were recorded using an A.E.I. model MS-9, MS-12 or MS-50 mass spectrometer.

Materials

Flash chromatography developed by Still[45] was used routinely for the purification and separation of the product mixtures. Nitrogen and argon were passed through a purification train of Fieser's solution,[90] concentrated sulfuric acid, and pellets of potassium hydroxide. Solvents used for reactions were purified as follows: tetrahydrofuran and 1,2-dimethoxyethane by distillation from a blue or purple solution of sodium benzophenone ketyl under an argon atmosphere; dimethyl sulfoxide and *N,N*- dimethylformamide by distillation over calcium hydride at reduced pressure; benzene, diethyl ether and toluene by distillation over lithium aluminium hydride; methylene chloride by distillation over phosphorus pentoxide. Hexane and ethyl acetate for chromatography were distilled prior to use.

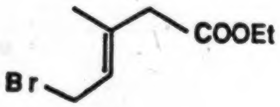
Ethyl 3-methyl-4-pentenoate (57)



57

A solution of crotyl alcohol (53.3 mL, 0.73 mol), triethyl orthoacetate (600 mL, 3.697 mol) and propionic acid (3.5 g, 0.047 mol) was heated at 138°C for 3 h, with a Dean-Stark apparatus to collect ethyl alcohol produced. The mixture was allowed to cool to room temperature and 750 mL of 1 M aqueous oxalic acid solution was slowly added. After being stirred at room temperature for 4 h, the mixture was extracted with ether. The ethereal extracts were washed with aqueous saturated sodium bicarbonate solution and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and concentrated. Distillation of the residue at room temperature at 3 mm pressure gave ester **57** (75.6 g, 72 %) as a yellow oil; ir (neat): 1730 (C=O) and 1640 cm^{-1} (C=C); ^1H nmr ∂: 5.81 (ddd, 1H, J = 18, J' = 10, J" = 7 Hz, -C**H**=), 5.02 (dm, 1H, J = 18 Hz, -CH=C**H**H), 4.98 (dm, 1H, J = 10 Hz, -CH=CH**H**), 4.12 (q, 2H, J = 7 Hz, $-COOCH_2-$), 2.68 (m, 1H, $-C\mathbf{H}(CH_3)-$), 2.27 (m, 2H, $-CH_2-$), 1.24 (t, 3H, J = 7 Hz, $-COOCH_2C\mathbf{H}_3$) and 1.05 (d, 3H, J = 7 Hz, $-CH_3$); hrms M^+: 142.0988 (calcd. for $C_8H_{14}O_2$: 142.0992).

Ethyl 5-bromo-3-methyl-3-pentenoate (58)

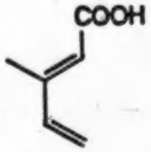


58

A solution of pentenoate **57** (66.31 g, 0.46 mol), *N*-bromosuccinimide (88.08 g, 0.46 mol) and azobisisobutyronitrile (1.6 g, 1 mmol) in carbon tetrachloride (1.5 L) was heated under reflux for 2 h under an argon atmosphere. The resulting mixture was cooled to 0°C. After being stirred at 0°C for 4 h, it was filtered. The residue was washed thoroughly with ice-cold carbon tetrachloride. The filtrate was washed with 1 M sodium thiosulfate solution and water. Drying, filtration and concentration gave the crude product which was distilled at

72°C and 1 mm pressure to give bromo-ester **58** (76.2 g, 75 % yield) as a 4:3 mixture of two geometric isomers; ir (neat): 1735 (C=O) and 1665 cm^{-1} (C=C); ^{1}H nmr ∂: 5.62 (m, 1H, =CH), 4.11 (q, 2H, J = 7 Hz, -COOCH$_2$-), 3.96 (d, 2H, J = 8 Hz,-CH$_2$Br), 3.09, 3.02 (both s, total 2H, -CH$_2$-COO-), 1.84,1.78 (both d, total 3H, J = 1 Hz, -CH$_3$) and 1.24 (t, 3H, J = 7 Hz, -COOCH$_2$CH$_3$); hrms m/z: 141.0912 [base peak; calcd. for $C_8H_{13}O_2$ (M$^+$-Br): 141.0914].

*3-Methyl-2,4-pentadienoic acid (**60**)*



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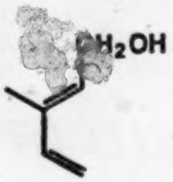
Bromo-ester **58** (24.8 g, 11.2 mmol) was added to a methanolic (285 mL) solution of sodium hydroxide (14.07 g, 0.35 mol) under an argon atmosphere. The resulting solution was heated under reflux for 24 h, poured into ice-cold water and extracted with ether. The ether extracts were discarded. The aqueous solution was carefully acidified with 1 N hydrochloric acid to pH 1. The solution was then extracted with methylene chloride. The organic extracts were washed with saturated aqueous sodium chloride solution, dried with anhydrous magnesium sulfate, filtered and concentrated to yield a yellow residue. Column chromatography of the residue on silica gel, eluting with 25% ethyl acetate in hexane, gave pure acid **58** (10 g, 80% yield) as a yellow oil; ir (neat): 1700 (C=O) and 1600 cm^{-1} (C=C); hrms M$^+$: 112.0523 (calcd. for $C_6H_8O_2$: 112.0523). The ^{1}H nmr spectrum showed two sets of signals integrated to a ratio of 3:1; the major set (*trans*-isomer) ∂: 6.42 (dd, 1H, J = 18, J' = 10 Hz, -C**H**=CH$_2$), 5.78 (bs, 1H, =C**H**-COOH), 5.60 (d, 1H , J = 18 Hz, =C**H**H), 5.40 (d, 1H, J = 10 Hz, =CH**H**) and 2.26 (d, 3H, J = 1 Hz, -CH$_3$); the minor set (*cis*-isomer) ∂: 7.80 (dd, 1H, J = 16, J' = 10 Hz, -C**H**=CH$_2$), 5.64 (bs, 1H, =C**H**-COOH), 5.48 (d, 1H, J = 16 Hz, =C**H**H), 5.38 (d, 1H, J = 10 Hz, =CH**H**), and 2.00 (d, 3H, J = 1 Hz, -CH$_3$).

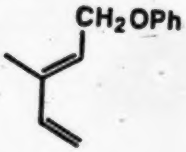
3-Methyl-2,4-pentadien-1-ol ***(62)***



62

At 0^{o}C, to a suspension of lithium aluminium hydride (2.37 g, 0.06 mol) in anhydrous ether (25 mL), was added dropwise a solution of acid **60** (9.36 g, 0.08 mol) in 15 mL of ether. After the addition (ca. 30 min), the reaction mixture was allowed to warm up to room temperature and was stirred for 8 h under an argon atmosphere. The mixture was then cooled to 0°C and treated successively with water (2.3 mL), 15% aqueous sodium hydroxide solution (2.3 mL) and water (6.9 mL) again. After being stirred for 15 min, the inorganic salts were removed by filteration and washed with ether. Concentration of the filtrate, followed by column chromatography of the residue on silica gel, eluting with 25% ethyl acetate in hexane, gave the alcohol **62** (4.8 g, 58% yield) as a yellow oil; ir ($CHCl_3$ cast): 3470 (OH) and 1600 cm^{-1} (C=C). The ^1H nmr spectrum showed two sets of signals integrated to a ratio of 3:1; the major set (*trans*-isomer) ∂: 6.76 (dd, 1H, J = 12, J' = 6 Hz, -C**H**=CH$_2$), 5.63 (d, 2H, J = 6 Hz, =C**H**H), 5.48 (d, 1H, J = 12 Hz, =CH**H**), 4.25 (d, 2H, J = 7 Hz, -C**H**$_2$OH) and 1.75 (d, 3H, J = 1 Hz, -CH$_3$); the minor set ∂: 6.76 (dd, 1H, J = 10, J' = 6 Hz, -C**H**=CH$_2$) 5.63 (d, 1H, J = 10 Hz, =C**H**H), 5.48 (d, 1H, J = 6 Hz, =CH**H**), 4.25 (d, 2H, J = 7 Hz, -C**H**$_2$OH) and 1.80 (d, 3H, J = 1 Hz, =C-CH$_3$)

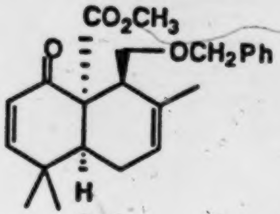
*5-Benzyloxy-3-methyl-1,3-pentadiene (**56**)*



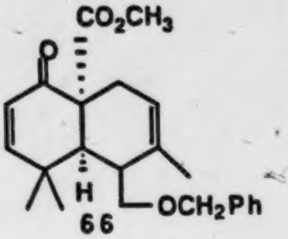
56

Sodium hydride (50% dispersion in oil, 1.35 g, 28 mmol) was washed three times with freshly distilled tetrahydrofuran (THF). It was then suspended in 10 mL of distilled THF and cooled to 0°C under an argon atmosphere. Alcohol **62** (2.3 g, 23 mmol) in 10 mL of THF was slowly added (ca. 10 min) with stirring. After 5 min, benzyl bromide (4.81 g, 23 mmol) was slowly added. The reaction mixture was allowed to warm up to room temperature and stirred at this temperature for 12 h. The mixture was then cooled to 0°C and ice-cold water was added dropwise until the excess of sodium hydride was destroyed. The resulting mixture was extracted with ether. The extracts were washed with 1 N hydrochloric acid and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. The residual oil was subjected to column chromatography on silica gel. Elution with 5% ethyl acetate in hexane gave pure **56** (3.6 g, 83 %) as a yellow liquid; ir (neat): 1600 (C=C) and 1110 cm^{-1} (C-O-C); hrms m/z: 189.1279 (M^+ + 1, calcd. for $C_{13}H_{17}O$: 189.1279), 91.0549 (base peak, calcd. for C_7H_7: 91.0549). The ^1H nmr spectrum showed two sets of signals, integrating to a ratio of 3:1; the major set (corresponding to the *trans*-isomer) ∂: 7.30 (m, 5H, aromatic), 6.40 (dd, 1H, J = 10, J' = 8 Hz, $-CH=CH_2$), 5.68 (t, 1H, J = 8 Hz, $=CH-CH_2O-$) and 1.74 (bs, 3H, $-CH_3$); the minor set (corresponding to the *cis*-isomer) ∂: 7.30 (m, 5H, aromatic), 6.72 (dd, 1H, J = 10, J'= 8 Hz, $-CH=CH_2O-$) and 1.86 (bs, 3H, $-CH_3$).

(1R, 6S*, 10S*)-10-Benzyloxymethyl-1-carbomethoxy-5,5,9-trimethylbicyclo[4.4.0]deca-3,8-dien-2-one* ***(65)*** and *(1R*, 6S*)-7-Benzyloxymethyl-1-carbomethoxy-5,5,8-trimethylbicyclo[4.4.0]deca-3,8-dien-2-one* ***(66)***



65



66

A. *Using ether as a solvent.*

Enone ester **45** (180 mg, 1 mmol) in 5 mL of dry ether was cooled to -20°C under an argon atmosphere. To this solution, was added anhydrous ferric chloride (165 mg, 1 mmol) and the resulting mixture was stirred with a mechanical stirrer. Diene **56** (380 mg, 2 mmol) in 10 mL of dry ether was slowly added to the reaction mixture over a period of 10 min. Stirring at -20°C was continued for 48 h, and the reaction mixture was warmed to room temperature and extracted with ether. The ether extracts were washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ethyl acetate in hexane, gave diene **56** (96 mg, 52% recovered) enriched now with the *cis*-isomer. Further elution with 10% ethyl acetate in hexane gave the Diels-Alder adduct **65** (199 mg, 84% yield, based on the consumed starting material) as a white solid; m.p. 80-82°C (hexane); ir (CHCl$_3$ cast): 1728 (ester C=O) and 1688 cm^{-1} (enone C=O); hrms M$^+$: 368.1962 (calcd. for $C_{23}H_{28}O_4$: 368.1988). ^{1}H nmr ∂: 7.32 (m, 5H, aromatic), 6.28 (dd, 1H, J = 11, J' = 2 Hz, -C**H**=CH-CO-), 5.88 (d, 1H, J = 11 Hz, -CH=C**H**-CO-), 5.25 (bs, 1H, CH$_3$-C=C**H**-), 4.48 (d, 1H, J = 12 Hz, -O-C**H**H-Ph), 4.42 (d, 1H, J = 12 Hz, -O-CH**H**-Ph), 4.16 (dd, 1H, J = 11, J' = 7 Hz, -C**H**H-OCH$_2$Ph), 3.54 (s, 3H, -OCH$_3$), 3.52 (dd, 1H, J = 11, J' = 4 Hz, -CH**H**-OCH$_2$Ph), 1.84 (bs, 3H, =C-CH$_3$), 1.14 and 1.10 (both s, 3H each, *gem*-dimethyl); ^{13}C nmr ∂: 196.09, 174.53, 152.61, 138.45, 132.97, 128.10, 127.65, 127.26, 126.74, 119.57, 72.43, 70.26, 60.10, 51.93, 46.65, 37.57, 27.82, 27.64, 27.16 and 20.76. Anal calcd. for $C_{23}H_{28}O_4$: C, 74.95; H, 7.66. Found: C, 74.79; H, 7.46.

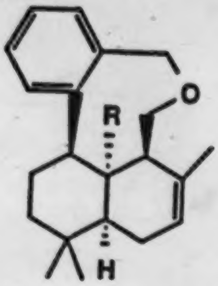
Further elution with 10% ethyl acetate in hexane gave the adduct **66** (20 mg, 8% yield,based on the consumed starting material) as a viscous oil; ir (neat): 1745 (ester C=O) and 1679 cm^{-1} (enone C=O); hrms M$^+$: 368.1987 (calcd. for $C_{23}H_{28}O_4$: 368.1988); ^{1}H nmr ∂: 7.30 (m, 5H, aromatic), 6.59 (d, 1H, J = 9 Hz, -C**H**=CH-CO-), 5.92 (dd, 1H, J = 9, J' = 2 Hz, -CH=C**H**-CO-), 5.46 (bs, 1H, CH$_3$-C=C**H**-), 4.50 (s, 2H, -O-CH$_2$Ph), 3.70 (s, 3H, -OCH$_3$), 3.68 (m, 2H, -C**H**$_2$-OCH$_2$Ph), 1.18 and 1.02 (both s, 3H each, *gem*-dimethyl); ^{13}C nmr ∂: 197.44, 172.85, 157.96, 138.41, 132.27, 128.25, 128.22, 127.57, 127.46, 123.90, 120.81, 119.79, 72.81, 68.55, 57.39, 52.40, 40.36, 37.56, 35.96, 31.69, 30.42, 24.24 and 23.51.

Final elution with 25% ethyl acetate in hexane gave (62 mg, 34% recovered)of the starting enone ester **45**

B. *Using dichloromethane as a solvent.*

Keto ester **45** (860 mg, 4.8 mmol) in 10 mL of dry dichloromethane was cooled to -20°C under an argon atmosphere. To this solution, was added anhydrous ferric chloride (0.77 g, 4.8 mmol) and the resulting solution was stirred with a mechanical stirrer. Diene **56** (1.80 g, 9.6 mmol) in 15 mL of dichloromethane was slowly added over a period of 5 min and stirring was continued for 24 h. The solution was warmed to room temperature. Water was added to the reaction mixture and the resulting solution was extracted with dichloromethane. The organic solution was washed with a saturated solution of aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with a 5% solution of ethyl acetate in hexane gave diene **56** (0.35 g, 20% recovered). Further elution with 10% ethyl acetate in hexane gave the keto ester **65** (0.97 g, 55% yield) as a white solid. Further elution with 10% ethyl acetate in hexane gave keto ester **66** (0.69 g, 39% yield). Compounds **65** and **66** thus obtained were found to be identical to those obtained as above.

(1R*,2S*,6S*,10S*)-2,3-(o-Benzeno)-8,12,12-trimethyl-5-oxatricyclo[9.3.1.0^{6,12}]pentadeca-8-ene (68)



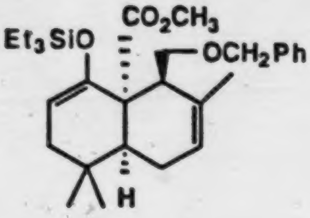
R = CO$_2$CH$_3$

68

Keto ester **65** (100 mg, 0.26 mmol) was dissolved in 3 mL of freshly distilled dichloromethane under an argon atmosphere at 0°C. To this solution, triethylsilane (ca. 1 mL) was added and the resulting solution was stirred for 5 min. Gaseous boron trifluoride was bubbled through the reaction mixture for 5 min. The reaction mixture was stirred for an additional period of 5 min and water was added. The resulting solution was extracted with dichloromethane and the extracts were washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, elution with 5% ethyl acetate in hexane, gave pure ether **68** (0.037 g, 39% yield); ir (CHCl$_3$ cast): 1725 cm^{-1} (C=O); hrms M$^+$: 354.2200 (calcd. for C$_{23}$H$_{30}$O$_3$: 354.2215); ^{1}H nmr ∂: 7.00 (m, 4H, aromatic), 5.70 (bs, 1H, CH$_3$-C=C**H**-), 4.68 (s, 2H, -

OCH_2Ph), 3.66 (s, 3H, $-OCH_3$), 1.80 (bs, 3H, $=C-CH_3$), 1.00 and 0.92 (each s, 3H each, *gem*-dimethyl).

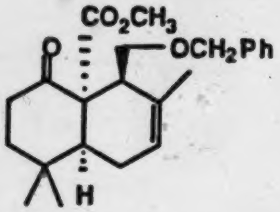
(1R,6S*,10S*)-10-Benzyloxymethyl-1-carbomethoxy-5,5,9-trimethyl-2-triethylsilyloxybicyclo[4.4.0]deca-2,8-diene* (**69**)



69

Finely divided keto-ester **65** (4.61 g, 12 mmol) was dissolved in 15 mL of freshly distilled benzene under an argon atmosphere. To this solution, triethylsilane (7.28 g, 0.06 mol) and tris-(triphenylphospine)rhodium(I) chloride (0.15 g, 0.6 mmol) were added. The mixture was stirred at room temperature for 24 h. At the end of the reaction period, the mixture was diluted with hexane and concentrated to give crude silyl enol ether **69**. Column chromatography on silica gel, eluting with a solution of 1% ethyl acetate in hexane, gave pure **69** (6.05 g, 100% yield) as a colourless oil; ir (neat): 1720 (C=O) and 1660 cm^{-1} (C=C); hrms M^+: 484.3013 (calcd. for $C_{29}H_{44}O_4Si$: 484.3009). ^1H nmr ∂: 7.30 (m, 5H, aromatic), 5.24 (bs, 1H, $CH_3-C=CH-$), 4.50 (m, 1H, $-O-C=CH-$) and 3.72 (s, 3H, $-OCH_3$).

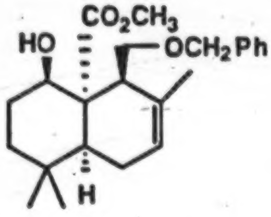
(1R,6S*,10S*)-10-Benzyloxymethyl-1-carbomethoxy-5,5,9-trimethylbicyclo[4.4.0]deca-8-en-2-one* (**70**)



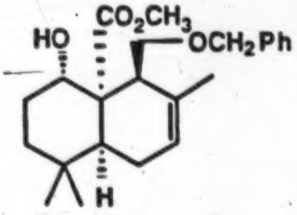
70

Pure silyl-enol ether **69** (6.05 g, 12 mmol) was dissolved in 20 mL of distilled tetrahydrofuran, and tetra-*n*-butylammonium fluoride (2.61 g, 12 mmol) was added dropwise to the resulting solution. The reaction mixture was stirred at room temperature for 4 h, after which period it was diluted with hexane and then concentrated. Column chromatography of the residue on silica gel, eluting with 5% ethyl acetate in hexane, gave pure keto-ester **70** (4.6 g, 100% yield) as a white solid; m.p. 40-42°C (hexane); ir ($CHCl_3$ cast): 1720 (ester C=O) and 1715 cm^{-1} (ketone C=O); hrms M^+: 370.2144 (calcd. for $C_{23}H_{30}O_4$: 370.2144); ^1H nmr ∂: 7.30 (m, 5H, aromatic), 5.30 (bs, 1H, CH_3-C=C**H**-), 4.46 (d, 1H, J = 13 Hz, -O-C**H**HPh), 4.40 (d, 1H, J = 13 Hz, -OCH**H**Ph), 4.00 (dd, 1H, J = 11, J' = 7 Hz, -C**H**H-OCH_2Ph), 3.60 (s, 3H, -OCH_3), 3.44 (dd, 1H, J = 11, J' = 7 Hz, -CH**H**-OCH_2Ph), 2.94 (m, 1H, -C**H**H-CO-), 2.70 (bs, 1H, -CH**H**-CO-), 1.80 (bs, 3H, =C-CH_3), 1.14 and 0.90 (each s, 3H each, *gem*-dimethyl); ^{13}C nmr ∂: 207.85, 174.69, 138.33, 133.49, 128.03, 127.50, 127.19, 119.44, 72.30, 69.59, 63.13, 51.83, 49.07, 46.53, 37.08, 35.82, 34.01, 27.97, 27.74, 25.14 and 20.63. Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.55%; H, 8.17. Found C, 74.46; H, 8.23.

(1R,2R*,6S*,10S*)-10-Benzyloxymethyl-1-carbomethoxy- 5,5,9-trimethylbicyclo[4.4.0]deca-8-en-2-ol* **(72)** *and (1R*,2S*,6S*, 10S*)-10-Benzyloxymethyl-1-carbomethoxy-5,5,9-trimethyl bicyclo[4.4.0]deca-8-en-2-ol* **(73)**



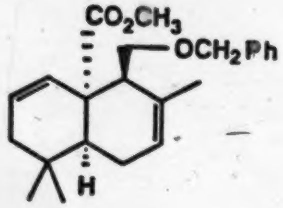
72



73

Keto ester **70** (160 mg, 4.4 mmol) was dissolved in 5 mL of distilled ether and the solution was cooled to 0°C under an argon atmosphere. To this ice-cold solution, diisobutylaluminium hydride (180 mg, 13.2 mmol) was slowly added. The reaction mixture was stirred at 0°C for 12 h and then ice-cold water was slowly added until evolution of hydrogen ceased. The resulting solution was extracted with ether. The extracts were washed with 1 N hydrochloric acid and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatrography of the residue on silica gel, eluting with 5% ethyl acetate in hexane, gave alcohol **72** (57 mg, 35% yield) as a colourless oil; ir ($CHCl_3$ cast): 3520 (OH) and 1717 cm^{-1} (C=O); hrms M^+: 372.2293 (calcd. for $C_{23}H_{32}O_4$: 372.2300); ^1H nmr ∂: 7.32 (m, 5H, aromatic), 5.32 (bs, 1H, CH_3-C=C**H**-), 4.46 (d, 1H, J = 12 Hz, -O-C**H**HPh), 4.40 (d, 1H, J = 12 Hz, -O-CH**H**Ph), 4.03 (dd, 1H, J = 8, J' = 5 Hz, -C**H**H-OCH_2Ph), 3.78 (m, 1H, -C**H**OH), 3.62 (s, 3H, -OCH_3), 3.46 (dd, 1H, J = 8, J' = 5 Hz, -CH**H**-OCH_2Ph), 1.86 (s, 3H, =C-CH_3), 1.18 and 0.96 (each s, 3H each, *gem*-dimethyl). Further elution with 7% ethyl acetate in hexane gave alcohol **73** (47 mg, 28% yield) as a colourless oil; ir ($CHCl_3$ cast): 3560 (O-H) and 1705 cm^{-1} (C=O); hrms M^+: 372.2292 (calcd. for $C_{23}H_{32}O_4$: 372.2201); ^1H nmr ∂: 7.28 (m, 5H, aromatic), 5.40 (bs, 1H, CH_3-C=C**H**-), 4.46 (d, 1H, J = 11 Hz, -O-C**H**HPh), 4.40 (d, 1H, J = 11 Hz, -O-CH**H**Ph), 3.84 (dd, 1H, J = 9, J' = 3 Hz, -C**H**H-OCH_2Ph), 3.60 (m, 1H, -C**H**OH), 3.58 (s, 3H, -OCH_3), 3.52 (dd, 1H, J = 9, J' = 5 Hz, -CH**H**-OCH_2Ph), 1.84 (s, 3H, =C-CH_3), 0.92 and 0.84 (each s, 3H each, *gem*-dimethyl).

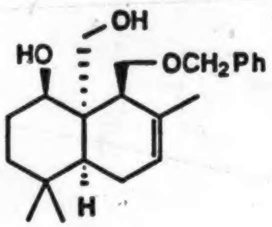
(1R,6S*,10S*)-10-Benzyloxymethyl-1-carbomethoxy-5,5,9-trimethylbicyclo[4.4.0]deca-2,8-diene* **(77)**



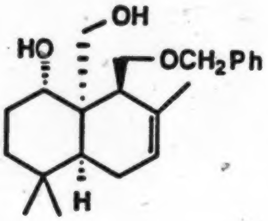
77

Alcohol **73** (80 mg, 0.22 mmol) was dissolved in 5 mL of distilled pyridine under an argon atmosphere. To this solution, phosphorous oxychloride (0.03 mL, 0.33 mmol) was added. The resulting solution was stirred at 80°C. After 8 h at this temperature, the reaction mixture was cooled to room temperature and diluted with water. The resulting solution was extracted with ether, and the ethereal extracts were washed with 1 N hydrochloric acid and a saturated solution of aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with a solution of 5% ethyl acetate in hexane, gave pure diene **77** (50 mg, 69% yield); ir ($CHCl_3$ cast): 1725 cm^{-1} (C=O); hrms M^+: 354.2210 (calcd. for $C_{23}H_{30}O_3$: 354.2195); ^1H nmr ∂: 7.22 (m, 5H, aromatic), 5.78 (bd, 1H, J = 6 Hz, $-CH_2CH=CH-$), 5.68 (m, 1H, $-CH_2CH=CH-$), 5.40 (bs, 1H, $CH_3-C=CH-$), 4.38 (s, 2H, $-OCH_2Ph$), 3.60 (s, 3H, $-OCH_3$), 1.64 (bs, 3H, $=C-CH_3$), 0.94 and 0.88 (each s, 3H each, *gem*-dimethyl).

(1R,2R*,6S*,10S*)-10-Benzyloxymethyl-1-hydroxymethyl-5,5,9-trimethylbicyclo[4.4.0]deca-8-ene-2-ol* (**74**) *and (1R*,2R*,6S*,10S*)-10-Benzyloxymethyl-1-hydroxymethyl-5,5,9-trimethyl bicyclo[4.4.0]deca-8-ene-2-ol* (**78**)



74



78

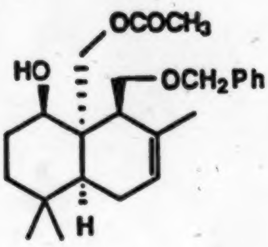
A. *Using Sodium Bis(methoxyethoxy)aluminium Hydride (Red-Al) as the Reducing Reagent*

Keto ester **70** (5.90 g, 15.9 mmol) was dissolved in 25 mL of dry ether under an argon atmosphere. The solution was cooled to 0°C and Red-Al (15.9 g, 79 mmol) in 25 mL of dry ether was added slowly (ca. 5 min). After being stirred at room temperature for 7 h, the reaction mixture was cooled to 0°C and ice-cold water was added cautiously until all the excess of Red-AL was destroyed. The resulting mixture was extracted with ether. The ether solution was washed with aqueous 1 N hydrochloric acid and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated. Column chromatography of the residue on silica gel, eluting with 20% ethyl acetate in hexane, gave pure diol **78** (530 mg, 9.7% yield); ir ($CHCl_3$ cast): 3424 (O-H) and 1363 cm^{-1} (CH_3); hrms m/z: 344.2397 (M^+, calcd. for $C_{22}H_{32}O_3$: 344.2351) and 326.2256 (M^+-18, calcd. for $C_{22}H_{30}O_2$: 326.2251); ^{1}H nmr ∂: 7.32 (m, 5H, aromatic), 5.80 (bs, 1H, CH_3-C=C**H**-), 4.80 (d, 1H, J = 12 Hz, -O-C**H**HPh), 4.62 (d, 1H, J = 12 Hz, -O-CH**H**Ph), 3.82 (d, 1H, J = 10 Hz, -C**H**HOH), 3.72 (d, 1H, J = 10 Hz, -CH**H**OH), 3.32 (dd, 1H, J = 11, J' = 3 Hz, -C**H**H-OCH_2Ph), 3.17 (dd, 1H, J = 11, J' = 3 Hz, -CH**H**-OCH_2Ph), 3.00 (bt, 1H, J= 9hz, -C**H**OH), 1.80 (t, 3H, J= 0.5 Hz, =C-CH_3), 0.84 and 0.76 (each s, 3H each, *gem*-dimethyl). Further elution with 20% ethyl acetate in hexane, gave pure diol **74** as a white solid (3.90 g, 71% yield); m.p. 90-92°C (hexane); ir ($CHCl_3$ cast): 3400 (O-H) and 1385 cm^{-1} (CH_3); hrms M^+: 344.2364 (calcd. for $C_{22}H_{32}O_3$: 344.2356); ^{1}H nmr ∂: 7.32 (m, 5H, aromatic), 5.44 (bs, 1H, CH_3-C=C**H**), 4.59 (d, 1H, J = 12 Hz, -O-C**H**HPh), 4.57 (d, 1H, J = 12 Hz, -O-CH**H**Ph), 4.10 (t, 1H, J = 10 Hz, -C**H**H-OCH_2Ph), 3.78 (dd, 1H, J = 10, J' = 3 Hz, -CH**H**-OCH_2Ph), 3.68 (d, 1H, J = 12 Hz, -C**H**HOH), 3.60 (m, 1H, -C**H**OH), 3.36 (d, 1H, J= 12 Hz, -CH**H**OH), 1.76 (bs, 3H, =C-CH_3), 0.94 and 0.78 (each s, 3H each, *gem*-dimethyl); ^{13}C nmr ∂: 136.49, 130.10, 128.39, 128.04, 123.39, 77.81, 76.37, 73.11, 69.28, 65.64, 45.05, 41.49, 41.12, 38.32, 33.31, 32.99, 29.54, 28.59, 24.61, 24.13, 22.96 and 15.12. *Anal* Calcd. for $C_{22}H_{32}O_3$: C, 76.69; H, 9.37; Found: C, 76.71; H, 9.40.

B. *Using Diisobutylaluminium Hydride (Dibal-H) as the Reducing Reagent*

Keto ester **70** (200 mg, 0.54 mmol) was dissolved in 5 mL of freshly distilled ether, and cooled to 0°C. To this solution, Dibal-H (380 mg, 2.7 mmol) in 10 mL of ether was added dropwise and the solution was gradually warmed up to room temperature. After stirring at room temperature for 10 h under an argon atmosphere, the solution was cooled again to 0°C. Water was slowly added to destroy the unreacted reducing reagent, and the resulting solution was extracted with ether. Ether extracts were washed with an aqueous solution of 1 N hydrochloric acid solution and a saturated solution of aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with a 25% solution of ethyl acetate in hexane, gave pure diol **74** (137 mg, 74% yield), which was shown to be identical in all respects to that obtained previously.

(1R,2R*,6S*,10S*)-1-Acetoxymethyl-10-benzyloxymethyl-5,5,9-trimethylbicyclo[4.4.0]deca-8-en-2-ol* (**79**)

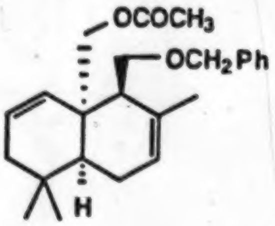


79

Diol **74** (140 mg, 3.9 mmol) was dissolved in 2 mL of distilled pyridine at room temperature. 4-(*N,N*-Dimethyl amino)pyridine (10 mg) and acetic anhydride (0.048 g, 4.7 mmol) were added to the solution. The reaction mixture was stirred at 80°C under an argon atmosphere for 12 h. It was then cooled to 0°C and an aqueous solution of 1 N hydrochloric acid was added. The resulting solution was extracted with ether, washed with a saturated solution of aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 15% ethyl acetate in hexane, gave pure acetate **79** (180 mg, 77% yield) as a white solid; m.p. 80-82°C (hexane); ir ($CHCl_3$ cast): 3420 (O-H) and 1741 cm^{-1} (C=O); hrms M^+: 386.2456 (calcd. for $C_{24}H_{34}O_4$: 386.2457); ^1H nmr ∂: 7.36 (m, 5H, aromatic), 5.55 (bs, 1H, CH_3-C=C**H**-), 4.58 (d, 1H, J= 11hz, -O-C**H**HPh), 4.54 (d, 1H, J= 11 Hz, -O-CH**H**Ph), 4.18 (d, 1H, J = 11 Hz, -C**H**H-OCOCH$_3$), 3.92 (d, 1H, J = 11 Hz, -CH**H**-OCOCH$_3$), 3.60 (bs, 1H, -C**H**OH), 2.12

(s, 3H, -CO-CH_3), 1.72 (s, 3H, =C-CH_3), 1.06 and 0.94 (each s, 3H each, *gem*-dimethyl).

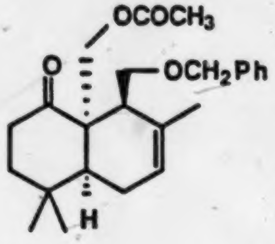
(1R,6S*,10S*)-1-Acetoxymethyl-10-benzeyloxymethyl-5,5,9-trimethylbicyclo[4.4.0]deca-2,8-diene (80)*



80

Acetate **79** (30 mg, 0.083 mmol) was dissolved in 1 mL of pyridine under an argon atmosphere. Phosphorus oxychloride (25 mg, 0.17 mmol) was added. The reaction mixture was heated at 80°C for 6 h. Water was added to the reaction mixture after it was cooled to room temperature. The resulting solution was extracted with ether and the extracts were washed with an aqueous solution of 1 N hydrochloric acid and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromotagraphy of the residue on silica gel, eluting with 5% ethyl acetate in hexane, gave diene **80** (16 mg, 53% yield) as a yellow oil; ir ($CHCl_3$ cast): 1741 (C=O), and 1235 cm^{-1} (-C-O-); hrms m/z: 308.2149 (M^+- 60, calcd. for $C_{22}H_{28}O$: 308.2140); cims m/z: 386 ($M + NH_4^+$); ^1H nmr ∂: 7.36 (m, 5H, aromatic), 5.82 (m, 1H, $-CH_2-C\mathbf{H}=C-$), 5.68 (d, 1H, J = 12 Hz, $CH_2-CH=C\mathbf{H}-$), 5.58 (bs, 1H, $CH_3-C=C\mathbf{H}-$), 4.50 (d, 1H, J = 11 Hz, $-OC\mathbf{H}HPh$), 4.44 (d, 1H, J = 11 Hz, $-OCH\mathbf{H}Ph$), 3.60 (dd, 1H, J = 10, J' = 3 Hz, $-C\mathbf{H}H-OCH_2Ph$), 3.38 (t, 1H, J = 10 Hz, $-CH\mathbf{H}-OCH_2Ph$), 2.08 (s, 3H, $-CO-CH_3$), 1.86 (s, 3H, $=C-CH_3$), 1.00 and 0.84 (each s, 3H each, *gem*-dimethyl).

(1R,6S*,10S*)-1-Acetoxymethyl-10-benzyloxymethyl-5,5,9-trimethylbicyclo[4.4.0]deca-8-en-2-one (**81**)*

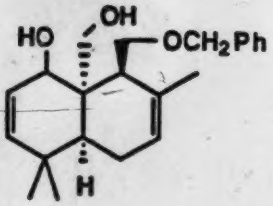


81

To a slurry of pyridinium chlorochromate (300 mg, 14 mmol) in 15 mL of dichloromethane, was added a solution of acetate **79** (118 mg, 4.5 mmol) in 5 mL of dichloromethane at room temperature. The mixture was stirred at room temperature for 4 h. It was then diluted with ether, filtered over magnesium sulfate and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ethyl acetate in hexane, gave ketone **81** (90 mg, 79% yield) as a viscous oil; ir ($CHCl_3$ cast): 1745 (ester C=O) and 1690 cm^{-1} (ketone C=O); hrms M^+: 384.2296 (calcd. for $C_{24}H_{32}O_4$: 384.2301); ^1H nmr ∂:

7.30 (m, 5H, aromatic), 5.56 (bs, 1H, CH_3-C=C**H**-), 4.46 (d, 1H, J = 12 Hz, -O-C**H**HPh), 4.38 (d, 1H, J = 12 Hz, -O-CH**H**Ph), 4.16 (d, 1H, J = 10 Hz, -C**H**H-OCOCH_3), 3.88 (d, 1H, J = 10 Hz, -CH**H**-OCOCH_3), 3.50 (dd, 1H, J = 8, J' = 4 Hz, -C**H**H-OCH_2Ph), 3.32 (t, 1H, J = 8 Hz, -CH**H**-OCH_2Ph), 2.02 (s, 3H, -COCH_3), 1.82 (s, 3H, =C-CH_3), 1.00 and 0.82 (each s, 3H each, *gem*-dimethyl).

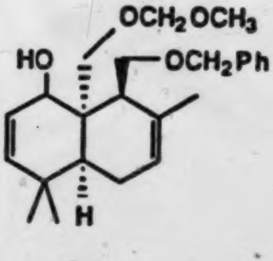
(1R,6S*,10S*)-10-Benzyloxymethyl-1-hydroxymethyl-5,5,9-trimethylbicyclo[4.4.0]deca-3,8-dien-2-ol* ***(82)***



82

To a solution of the Diels-Alder adduct **65** (1.47 g, 4 mmol) in 15 mL of dry ether at 0°C, was added Red-Al (4.05 g, 0.02 mol) in 10 mL of ether. The reaction mixture was warmed up to 27°C. After being stirred at this temperature for 5 h, the reaction mixture was cooled again to 0°C. Ice-cold water was added slowly to destroy excess Red-Al and the resulting solution was extracted with ether. Ethereal extracts were washed with an aqueous solution of 1 N hydrochloric acid and a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 20% ethyl acetate in hexane, gave pure diol **82** (1.02 g, 74% yield) as a white solid; ir ($CHCl_3$ cast): 3400 cm^{-1} (O-H); cims m/z: 343 (M^++1); ^{1}H nmr ∂: 7.28 (m, 5H, aromatic), 5.56 (dd, 1H, J = 8, J' = 2 Hz, -CH=C**H**-CHOH-), 5.40 (bs, 1H, CH_3-C=C**H**-), 5.26 (dd, 1H, J = 8, J' = 1 Hz, -C**H**=CH-CHOH-), 4.48 (d, 1H, J = 12 Hz, -O-C**H**HPh), 4.38 (d, 1H, J = 12 Hz, -O-CH**H**Ph), 4.26 (m, 1H, -C**H**OH), 4.13 (d, 1H, J = 10 Hz, -C**H**HOH), 3.70 (t, J = 10 Hz, -C**H**H-OCH$_2$Ph), 3.50 (dd, 1H, J = 10, J' = 4 Hz, -CH**H**-OCH$_2$Ph), 3.38 (d, 1H, J = 10 Hz, -CH**H**OH), 1.72 (bs, 3H, =C-CH$_3$), 0.98 and 0.82 (each s, 3H each, *gem*-dimethyl). Anal Calcd. for $C_{22}H_{30}O_3$: C, 77.14; H, 8.83; Found: C, 76.74; H, 8.93.

(1R,6S*,10S*)-10-Benzyloxymethyl-1-methoxymethoxymethyl-5,5,9-trimethylbicyclo[4.4.0]dec-3,8-dien-2-ol* (**83**)

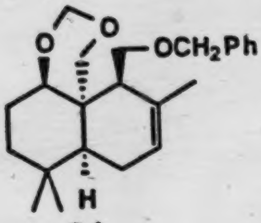


83

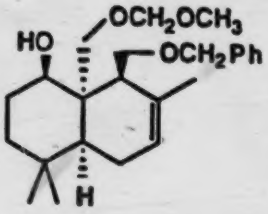
Sodium hydride (50% dispersion in oil, 118 mg, 2.4 mmol) was washed three times with freshly distilled 1,2-

dimethoxyethane and was then suspended in 10 mL of dry 1,2-dimethoxyethane under an argon atmosphere. Diol **82** (170 mg, 0.5 mmol) in 5 mL of 1,2-dimethoxyethane was slowly added to the suspension. The resulting mixture was stirred at 0°C for 5 min. Chloromethyl methyl ether (0.05 mL, 0.6 mmol) was added and the reaction mixture was gradually warmed up to room temperature. The resulting solution was stirred for 1 h, and cooled again to 0°C. Water was added to destroy unreacted sodium hydride. The resulting solution was extracted with ether, washed with a saturated solution of aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with a 10% solution of ethyl acetate in hexane, gave pure ether **83** (120 mg, 61% yield); ir ($CHCl_3$ cast): 3420 cm^{-1} (OH); hrms M^+: 386.2451 (calcd. for $C_{24}H_{34}O_4$: 386.2457); ^1H nmr ∂: 7.32 (s, 5H, aromatic), 5.70 (dm, 1H, J = 10 Hz, -C**H**=CH-CHOH), 5.48 (bs, 1H, CH_3-C=C**H**-), 5.30 (dd, 1H, J = 10, J' = 2 Hz, -CH=C**H**-CHOH), 4.62 (s, 2H, -OCH_2Ph), 3.16 (s, 3H, -OCH_3), 1.72 (bs, 3H, =C-CH_3), 1.04 and 0.86 (each s, 3H each, *gem*-dimethyl).

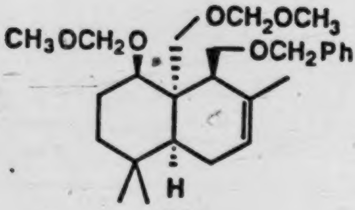
(1R,2R*,6S*,10S*)-10-Benzyloxymethyl-1-methoxymethoxy methyl-5,5,9-trimethyl bicyclo[4.4.0]dec-8-en-2-ol* (**85**)



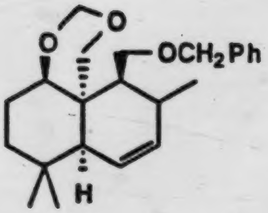
84



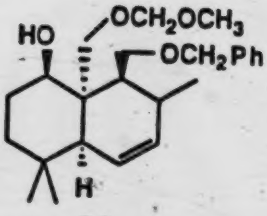
85



86



87



88

A. *Using Sodium Hydride as a Base*

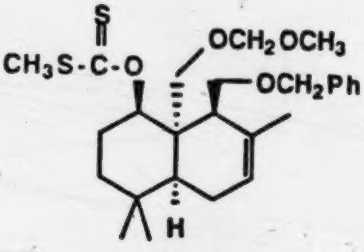
Sodium hydride (50% dispersion in oil, 550 mg, 0.01 mol) was washed twice with freshly distilled 1,2-dimethoxyethane under an argon atmosphere, suspended in 10 mL of dry 1,2-dimethoxyethane and cooled to -10°C. Diol **74** (1.20 g, 3.5 mmol) in 5 mL of 1,2-dimethoxyethane was then slowly added and the resulting mixture was stirred for 10 min. Chloromethyl methyl ether (0.32 mL, 4.2 mmol) was slowly added. After 30 min, water was slowly added to the reaction mixture and the temperature was slowly raised to room temperature. The resulting solution was extracted with ether. The extracts were washed with a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ethyl acetate in hexane, gave acetal **84** (490 mg, 59% yield); ir (CHCl$_3$ cast): 1106 cm^{-1} (C-O-C); hrms M$^+$: 356.2355 (calcd. for $C_{23}H_{32}O_3$: 356.2352); ^{1}H nmr ∂: 7.34 (m, 5H, aromatic), 5.34 (bs, 1H, CH$_3$-C=C**H**-), 5.14 (d, 1H, J = 6 Hz, -O-C**H**H-O-), 4.80 (d, 1H, J = 6 Hz, -OCH**H**O-), 4.56 (d, 1H, J = 12 Hz, -OC**H**HPh), 4.50 (d, 1H, J = 12 Hz, -OCH**H**Ph), 4.25 (dd, 1H, J = 10, J' = 4 Hz, -C**H**H-OCH$_2$Ph), 3.92 (dd, 1H, J = 10, J' = 6 Hz,-CH**H**-OCH$_2$Ph), 3.78 (d, 1H, J = 10 Hz, -C**H**H-OCH$_2$O-), 3.36 (dd, 1H, J = 13, J' = 2 Hz, -OCH$_2$-OC**H**-), 3.13 (d, 1H, J = 10 Hz, -CH**H**-OCH$_2$O), 1.81 (bs, 3H, =C-CH$_3$), 0.86 and 0.78 (each s, 3H each, *gem*-dimethyl). Further elution with 7% ethyl acetate gave ether **86** (0.14 g, 9% yield); ir (CHCl$_3$ cast): 1147 and 1109 cm^{-1} (C-O-C); cims m/z: 450 (M + NH$_4^+$); hrms m/z: 326.2242 (M$^+$ - 106, calcd. for $C_{22}H_{30}O_2$: 326.2246); ^{1}H nmr ∂: 7.32 (m, 5H, aromatic), 5.32 (bs, 1H, CH$_3$-C=C**H**-), 4.70 (d, 1H, J = 12 Hz, -O-C**H**H-Ph), 4.64 (d, 1H, J = 12 Hz, -O-CH**H**-Ph), 4.62, 4.52 (each s, 2H each, 2 x -O-CH$_2$-O-), 4.40 (dd, 1H, J = 9, J' = 2 Hz, -C**H**H-OCH$_2$Ph), 3.78 (dd, 1H, J = 11, J' = 6 Hz, -C**H**-OCH$_2$O-), 3.58 (t, 1H, J = 9 Hz, -CH**H**-OCH$_2$Ph),3.48 (d, 1H, J = 10 Hz, -C**H**H-OCH$_2$O-), 3.36, 3.34 (each s, 3H each, 2 x -OCH$_3$), 3.29 (d, 1H, J = 10 Hz, -CH**H**-OCH$_2$O-), 1.79 (s, 3H, =C-CH$_3$), 0.92 and 0.72 (each s, 3H each, *gem*-dimethyl). Further elution with 10% ethyl acetate in hexane gave hydroxy ether **85** (351 mg, 26% yield) as a white solid; m.p. 55- 56°C (hexane); ^{1}H nmr ∂: 7.32 (m, 5H, aromatic), 5.49 (bs, 1H, CH_3-C=C**H**-), 4.60 (d, 1H, J = 9 Hz, -O-C**H**H-Ph), 4.58 (d, 1H, J = 9 Hz, -O-CH**H**-Ph), 4.54 (d, 1H, J = 7 Hz, -O-C**H**H-O-), 4.50 (d, 1H, J = 7 Hz, -O-CH**H**-O-), 4.03 (dd, 1H, J = 10, J' = 7 Hz, -C**H**H-OCH_2Ph), 3.74 (dd, 1H, J = 10, J' = 2 Hz, -CH**H**-OCH_2Ph), 3.64 (d, 1H, J = 10 Hz, -C**H**H-OCH_2O-), 3.32 (s, 3H, -OCH_3), 3.24 (d, 1H, J= 10 Hz, -CH**H**-OCH_2-O-), 1.70 (bs, 3H, =C-CH_3), 1.00 and 0.82 (each s, 3H each, *gem*-dimethyl); ir ($CHCl_3$ cast): 3460 (OH), 1096 and 1041 cm^{-1} (C-O-C); hrms M$^+$: 388.2614 (calcd. for $C_{24}H_{36}O_4$: 388.2614); ^{13}C nmr ∂: 137.05, 131.02, 128.43, 128.01, 127.90, 124.23, 96.86, 73.35, 72.81, 71.42, 68.78, 55.41, 44.94, 44.12, 39.57, 35.03, 33.33, 32.09, 27.89, 27.20, 25.45 and 22.59. Anal Calcd. for $C_{24}H_{36}O_4$: C, 74.17; H, 9.34; Found: C, 73.86; H, 9.21. On increasing the polarity of the eluent to 20% ethyl acetate in hexane gave acetal **87** (80 mg, 7% yield) was obtained; ir (neat): 1110 cm^{-1} (C-O-C); hrms M$^+$: 356.2344 (calcd. for $C_{23}H_{32}O_3$: 356.2351); ^{1}H nmr ∂: 7.28 (m, 5H, aromatic), 5.52 (m, 1H, CH_3CH-C**H**=CH-), 5.42 (bd, 1H, J = 9 Hz, CH_3CH-CH=C**H**-), 5.15 (d, 1H, J = 6 Hz, -OC**H**HO-), 4.84 (d, 1H, J = 6 Hz, -OCH**H**O-), 4.50 (d, 1H, J = 11 Hz, -OC**H**HPh), 4.46 (d, 1H, J = 11 Hz, -OCH**H**Ph), 1.19 (d, 3H, J = 7 Hz, -CH-C**H**$_3$), 0.99 and 0.74 (each s, 3H each, *gem*-dimethyl). On further elution hydroxy ether **88** (70 mg, 5% yield) was isolated; ir (neat): 3500 cm^{-1} (OH); hrms M$^+$: 388.2606 (calcd. for $C_{24}H_{36}O_4$:

388.2614); ^{1}H nmr ∂: 7.26 (m, 5H, aromatic), 5.56 (m, 1H, $CH_3CH\text{-}C\mathbf{H}\text{=}CH\text{-}$), 5.38 (bd, 1H, J = 8 Hz $CH_3CH\text{-}CH\text{=}C\mathbf{H}\text{-}$), 4.60 (d, 1H, J = 11 Hz, -OC**H**HPh), 4.56 (d, 1H, J = 11 Hz, -OCH**H**Ph), 4.46 (d, 1H, J = 7 Hz, -OC**H**HO-), 4.44 (d, 1H, J = 7 Hz, -OCH**H**O-), 3.83 (m, 2H, $\text{-}C\mathbf{H}_2\text{-}OCH_2Ph$), 3.64 (d, 1H, J = 8 Hz, -$C\mathbf{H}H\text{-}OCH_2O\text{-}$), 3.35 (s, 3H, $\text{-}OCH_3$), 3.23 (d, 1H, J = 4 Hz, -C**H**OH), 3.09 (d, 1H, J = 8 Hz, $\text{-}CH\mathbf{H}\text{-}OCH_2O\text{-}$), 1.13 (d, 3H, J = 7 Hz, $\text{-}CH\text{-}C\mathbf{H}_3$), 1.00 and 0.76 (each s, 3H each, *gem*-dimethyl).

B. Using Potassium Hydride as a Base.

Potassium hydride (35% dispersion in oil, 405 mg, 0.01 mol) was washed twice with freshly distilled 1,2-dimethoxyethane under an argon atmosphere. It was then suspended in 10 mL of 1,2-dimethoxyethane and cooled to -10°C. Diol **74** (694 mg, 0.002mol) in 2 mL of 1,2-dimethoxyethane was then slowly added and the mixture was stirred for 10 min. Chloromethyl methyl ether (195 mg, 2.4 mmol) was added. After 15 min, water was slowly added to the reaction mixture and the temperature was gradually raised to room temperature. The resulting solution was extracted with ether and the extracts were washed with an aqueous solution of saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromotagraphy of the residue on silica gel, eluting with 5% ethyl acetate in hexane gave ether **86** (178 mg, 21% yield) as a colourless paste, identical in all respects to the one described above. Further elution with 10% ethyl acetate in hexane gave hydroxy ether **85** (540 mg, 70% yield) as a white solid. The compound thus obtained was shown to possess the same physical properties as the one described previously.

(1R,2S*,6S*,10R*)-2-Benzyloxymethyl-10-methylmercapto thionocarbonyloxy-1-methoxymethoxymethyl-3,7,7-trimethyl bicyclo[4.4.0]dec-3-ene (**89**)*



89

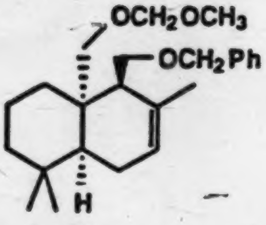
A. *1,2-Dimethoxyethane as Solvent*

Sodium hydride (50% dispersion in oil, 470 mg, 0.01 mol) was washed 3 times with freshly distlled 1,2-dimethoxyethane. It was then suspended in 10 mL of 1,2-dimethoxyethane under an argon atmosphere and cooled to 0°C. A solution of alcohol **85** (763 mg, 2.0 mmol) in 10 mL of 1,2-dimethoxyethane was slowly added to the suspension. After stirring for 10 min carbon disulfide (1.49 g, 20 mmol) and methyl iodide (2.71 g, 20 mmol) were added. The reaction mixture was stirred at room temperature for 6 h, and again cooled to 0°C. Water was added slowly to the reaction mixture and the resulting solution was extracted with dichloromethane. Organic layer was washed respectively with aqueous 1 N hydrochloric acid and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ethyl acetate in hexane, gave pure **89** (0.876 g, 94% yield) as a pale yellow oil; ^{1}H nmr ∂: 7.30 (m, 5H, aromatic), 5.82 (dd, 1H, J = 10, J' = 5 Hz, -CH-OCS-), 5.35 (bs, 1H, CH_3-C=C**H**-), 4.60 (d, 1H, J = 8 Hz, -O-C**H**HPh), 4.52 (d, 1H, J = 8 Hz, -O-CH**H**Ph), 4.50 (d, 1H, J = 8 Hz, -O-C**H**H-O-), 4.48 (d, 1H, J = 8 Hz, -O-CH**H**-O-), 4.16 (dd, 1H, J = 9, J' = 2 Hz, -C**H**H-OCH_2Ph), 3.58 (dd, 1H, J = 9, J' = 7 Hz, -CH**H**-OCH_2Ph), 3.37 (d, 1H, J = 12 Hz, -C**H**H-OCH_2O-), 3.30 (s,3H, -OCH_3), 3.29 (d, 1H, J = 12 Hz, -CH**H**-OCH_2O-), 2.50 (s,3H, -SCH_3), 1.76 (s, 3H, =C-CH_3), 1.00 and 0.80 (each s, 3H each, *gem*-dimethyl); ^{13}C nmr ∂: 133.97, 128.21, 127.59, 120.96, 97.06, 84.24, 77.63, 76.37, 72.97, 72.34,72.29, 55.47, 44.34, 43.97, 39.14, 36.45, 32.92, 32.09, 24.66, 23.88, 23.46 and 18.54; ir ($CHCl_3$ cast): 1223 (C=S) and 1048 cm^{-1} (C-O-C); cims m/z: 496 (M + NH_4^+); hrms m/z: 431.2247 (M^+-47, calcd. for $C_{25}H_{35}O_5S$: 431.2256), 371.2571 (M^+-108, calcd. for $C_{24}H_{35}O_3$: 371.2586).

B. *Using Tetrahydrofuran as Solvent*

Sodium hydride (50% dispersion in oil, 130 mg, 2.6 mmol) was washed 3 times with freshly distlled tetrahydrofuran. It was then suspended in 10 mL of tetrahydrofuran under an argon atmosphere and a solution of alcohol **85** (340 mg, 0.9 mmol) in 10 mL of tetrahydrofuran was slowly added. After stirring 10 min, carbon disulfide (0.2 mL, 3.5 mmol) and methyl iodide (0.5 g, 3.6 mmol) were added. The reaction mixture was stirred at room temperature for 24 h, and cooled to 0°C. Water was added slowly to the reaction mixture and the resulting solution was extracted with dichloromethane. The organic layer was washed with an aqueous solution of 1 N hydrochloric acid and a saturated solution of aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ethyl acetate in hexane, gave pure **89** (70 mg, 31% yield, based on consumed starting material) as a pale yellow oil. The compound thus obtained was found to be identical in all respects to the one isolated before. Further elution with 15% ethyl acetate in hexane gave pure hydroxy ether **85** (150 mg, 44% recovery).

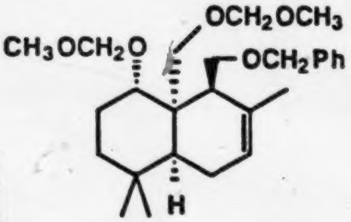
(1S,2S*,6S*)-2-Benzyloxymethyl-1-methoxymethoxymethyl-3,7,7,-trimethylbicyclo[4.4.0]deca-3-ene **(91)** From Xanthate **89***



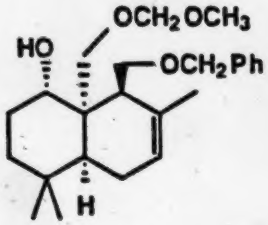
91

The xanthate **89** (980 mg, 2 mmol), tri-*n*-butyltin hydride (1.75 g, 6 mmol) and azobisisobutyronitrile (100 mg) were dissolved in freshly distilled toluene (20 mL). The solution was degassed by bubbling argon through it for 20 min. The resulting solution was then refluxed for 3 h at 120°C. The reaction mixture was cooled to room temperature and concentrated. The residue on column chromatography over silica gel, eluting with 2% ethyl acetate in hexane, gave pure **91** as a colourless viscous oil (740 mg, 97% yield); ir ($CHCl_3$ cast): 1100 and 1050 cm^{-1} (-C-O-C); cims m/z: 390 (M + NH_4^+); hrms M^+: 372.2678 (calcd. for $C_{24}H_{36}O_3$: 372.2669); ^1H nmr ∂: 7.24 (m, 5H, aromatic), 5.38 (bs, 1H, CH_3-C=C**H**-), 4.53 (d, 1H, J = 6 Hz, -O-C**H**HPh), 4.48 (d, 1H, J = 6 Hz, -O-CH**H**Ph), 4.40 (d, 1H, J = 12 Hz, -O-C**H**H-O-), 4.36 (d, 1H, J = 12 Hz, -O-CH**H**-O-), 3.62 (dd, 1H, J = 10, J' = 5 Hz, -C**H**H-OCH_2Ph), 3.45 (d, 1H, J = 10 Hz, -C**H**H-OCH_2O-), 3.40 (dd, 1H, J = 10, J' = 5 Hz, -CH**H**-OCH_2Ph), 3.28 (d, 1H, J = 10 Hz, -CH**H**-OCH_2O-), 3.26 (s, 3H, -OCH_3), 1.66 (bs, 3H, =C-CH_3), 0.94 and 0.74 (each s, 3H each, *gem*-dimethyl); ^{13}C nmr ∂: 138.93, 134.34, 128.23, 127.61, 122.08, 96.90, 74.24, 72.94, 70.03, 55.41, 45.64, 42.31, 40.20, 36.05, 33.33, 31.45, 27.95, 25.93, 24.43, 22.87, and 18.77. *Anal* Calcd. for $C_{24}H_{36}O_3$: C, 77.36; H, 9.74; Found C, 76.97; H, 9.57.

(1R,2S*,6S*,10S*)-10-Benzyloxymethyl-1-methoxymethoxymethyl-5,5,9-trimethylbicyclo[4.4.0]dec-8-ene-2-ol* ***(93)***



92

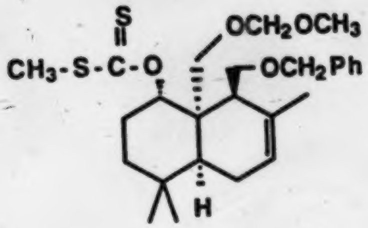


93

Potassium hydride (35% dispersion in oil, 390 mg, 7.5 mmol) was washed twice with freshly distilled 1,2-dimethoxyethane under an argon atmosphere. It was then suspended in 10 mL of 1,2-dimethoxyethane and cooled to -10°C. Diol **78** (530 mg, 1.5 mmol) in 2 mL of 1,2-dimethoxyethane was then slowly added and the mixture was stirred for 10 min. Chloromethyl methyl ether (160 mg, 2.3 mmol) was slowly added. After 15 min water was slowly added to the reaction mixture and the temperature was gradually raised to room temperature. The resulting solution was extracted with ether. The extracts were washed with aqueous saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated.

Column chromotagraphy of the residue on silica gel, eluting with 5% ethyl acetate in hexane, gave ether **92** (440 mg, 68% yield); ir ($CHCl_3$): 1109 and 1051 cm^{-1} (C-O-C); hrms M$^+$: 432.2872 (calcd. for $C_{26}H_{40}O_5$: 432.2876); ^{1}H nmr ∂: 7.32 (m, 5H, aromatic), 5.32 (bs, 1H, CH_3-C=C**H**-), 4.70 (d, 1H, J = 7 Hz, -OC**H**HPh), 4.62 (d, 1H, J = 7 Hz, -OCH**H**Ph), 4.60 and 4.50 (each s, 2H each, 2 x -O-CH_2-O-), 4.41 (d, 1H, J = 9 Hz, -C**H**H-OCH_2O-), 3.78 (dd, 1H, J = 12, J' = 6 Hz, -C**H**H-OCH_2Ph), 3.56 (dd, 1H, J = 7, J' = 6 Hz, -CH**H**-OCH_2Ph), 3.42 (d, 1H, J = 9 Hz, -CH**H**-OCH_2O-), 3.34 and 3.32 (each s, 3H each, 2 x -OCH_3), 1.78 (bs, 3H, =C-CH_3), 0.90 and 0.72 (each s, 3H each, *gem*-dimethyl). Further elution with 10% ethyl acetate in hexane, gave pure hydroxy ether **93** (145 mg, 26% yield); ir ($CHCl_3$ cast): 3450 (OH), 1109 cm^{-1} (C-O-C); hrms m/z: 356.2350 (M$^+$-32, calcd. for $C_{23}H_{32}O_3$: 356.2350); ^{1}H nmr ∂: 7.32 (s, 5H, aromatic), 5.52 (bs, 1H, CH_3-C=C**H**-), 4.58 (s, 2H, -OCH_2Ph), 4.52 (s, 2H, -OCH_2O-), 3.38 (s, 3H, -OCH_3), 1.80 (bs, 3H, =C-CH_3), 1.06 and 0.88 (each s, 3H each, *gem*-dimethyl).

(1R,2S*,6S*,10S*)-2-Benzyloxymethyl-10-methylmercaptothionocarbonyloxy-1-methoxymethoxymethyl-3,7,7-trimethylbicyclo[4.4.0]dec-3-ene* ***(94)***



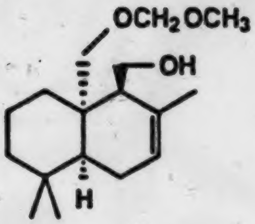
94

Sodium hydride (50% dispersion in oil, 90 mg, 1.86 mmol) was washed 3 times with freshly distilled 1,2-dimethoxyethane. It was then suspended in 10 mL of 1,2-dimethoxyethane under an argon atmosphere and cooled to 0°C. A solution of alcohol **93** (140 mg, 0.37 mmol) in 5 mL of 1,2-dimethoxyethane was added to the suspension. The resulting solution was stirred for 10 min and then carbon disulfide (0.2 mL, 3.7 mmol) and methyl iodide (0.25 mL, 3.7 mmol) were added. The reaction mixture was stirred at room temperature for 6 h, and then cooled to 0°C. Water was added slowly to the reaction mixture and the resulting solution was extracted with dichloromethane. The organic layer was washed with aqueous 1 N hydrochloric acid and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ethyl acetate in hexane, gave pure **94** (0.15 g, 83% yield) as a pale yellow oil; ir ($CHCl_3$ cast): 1223 cm^{-1} (C=S); ^1H nmr ∂: 7.30 (m, 5H, aromatic), 6.08 (dd, 1H, J = 7, J' = 5 Hz, -CH-OC=S), 5.50 (bs, 1H, CH_3-C=CH-), 4.58 (s, 2H, -OCH_2Ph), 4.50 (d, 1H, J = 12 Hz, -OCHHO-), 4.44 (d, 1H, J = 12 Hz, -OCH**H**O-), 3.76 (dd, 1H, J = 10, J' = 5 Hz, -C**H**H-OCH_2Ph), 3.65 (d, 1H, J = 9 Hz, -C**H**H-OCH_2O-), 3.54 (dd, 1H, J = 10, J' = 7 Hz, -CH**H**-OCH_2Ph), 3.52 (d, 1H, J = 9 Hz, -CH**H**-OCH_2O-), 3.34 (s, 3H, -OCH_3), 2.52 (s, 3H, -SCH_3), 1.76 (bs, 3H, =C-CH_3), 1.00 and 0.86 (each s, 3H each, *gem*-dimethyl).

(1S,2S*,6S*)-2-Benzyloxymethyl-1-methoxymethoxymethyl-3,7,7-trimethylbicyclo[4.4.0]dec-3-ene* ***(91)*** *from Xanthate* ***94***

The xanthate **94** (150 mg, 0.31 mmol), tri-*n*-butyltin hydride (140 mg, 0.46 mmol) and azobisisobutyronitrile (15 mg) were dissolved in freshly distilled toluene (10 mL). The solution was degassed by bubbling argon gas through it for 20 min. The resulting solution was then refluxed for 3 h at 120°C. The reaction mixture was cooled to room temperature and concentrated. The residue, on column chromatography on silica gel, eluting with 2% ethyl acetate in hexane, gave pure **91** as a colourless viscous oil (114 mg, 98% yield). The compound thus obtained was found to be identical with the one obtained before.

(1S,2S*,6S*)-2-Hydroxymethyl-1-methoxymethoxymethyl-3,7,7-trimethylbicyclo[4.4.0]dec-3-ene* **(95)**



95

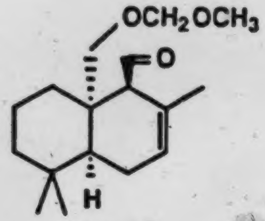
A. *Using Liquid Ammonia*

At -78°C, a solution of benzyl ether **91** (640 mg, 1.7 mmol) in 5 mL of dry ether and t-butyl alcohol (ca. 5 drops) was added, over a period of 5 min, to freshly distilled ammonia (20 mL) under an argon atmosphere. Lithium metal (200 mg, 0.028 g-atom) was added in small portions over a period of 5 min. The resulting blue solution was stirred for 5 h, during which period the blue colour was discharged. Methanol was added dropwise and the excess of ammonia was allowed to evoporate at room temperature. Water was added and the resulting mixture was extracted with ether. The ethereal extracts were washed with a saturated solution of aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 25% ethyl acetate in hexane gave pure alcohol **55** (400 mg, 82% yield) as a colourless paste; ir ($CHCl_3$ cast): 3450 (O-H), 1107 cm^{-1} (C-O-C); cims m/z: 300 (M + $NH4^+$); hrms m/z: 219.1747 (M^+ - 63, calcd. for $C_{15}H_{23}O$: 219.1749), and 201.1646 (M^+ - 81, calcd. for $C_{15}H_{21}$: 201.1643); ^1H nmr ∂: 5.64 (bs, 1H, $CH_3-C{=}C\mathbf{H}-$), 4.64 (s, 2H, $-O-CH_2-O-$), 3.82 (m, 2H, $-C\mathbf{H}_2OH$), 3.56 (d, 1H, J = 11 Hz, $-C\mathbf{H}H-OCH_2O-$), 3.42 (d, 1H, J = 11 Hz, $-CH\mathbf{H}-OCH_2O-$), 3.38 (s, 3H, $-OCH_3$), 1.80 (d, 3H, J = 1 Hz, $=C-C\mathbf{H}_3$), 1.06 and 0.90 (each s, 3H each, *gem*-dimethyl); ^{13}C nmr ∂: 133.63, 124.08, 96.82, 74.25, 61.27, 55.42, 48.61, 43.33, 40.63, 35.52, 33.28, 31.30, 28.69, 24.42, 23.09 and 22.86. Anal Calcd. for $C_{17}H_{30}O_3$: C, 72.28; H, 10.71; Found: C, 71.97; H, 10.38.

B. *Using Diethylamine*

At -10°C, a solution of benzyl ether **91** (500 mg, 1.3 mmol) in 5 mL of dry ether and *t*-butyl alcohol (ca. 5 drops) was added, over a period of 5 min, to freshly distilled diethylamine (20 mL) under an argon atmosphere. Lithium metal (200 mg, 0.028 g-atom) was added in small portions over a period of 5 min. The resulting blue solution was stirred for 5 h, during which period the blue colour was discharged. Methanol was added dropwise and the excess of amine was allowed to evaporate at room temperature. Water was added and the resulting solution was extracted with ether. The ethereal extracts were washed with a saturated solution of aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 25% ethyl acetate in hexane, gave pure alcohol **55** (400 mg, 82% yield) as a colourless paste. The compound thus obtained was readily identified with the compound obtained previously.

(1S,2S*,6S*)-2-Formyl-1-methoxymethoxymethyl-3,7,7-trimethylbicyclo[4.4.0]dec-3-ene (**96**)*



96

A. *Using Swern's Oxidation Procedure*

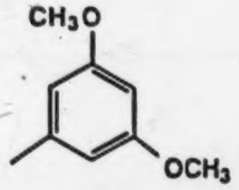
A solution of dimethyl sulfoxide (0.26 mL, 3.7 mmol) in dichloromethane (2 mL) was added dropwise to a solution of oxalyl chloride (0.23 mL, 2.7 mmol) in 2 mL dichloromethane at -78°C under an argon atmosphere. The mixture was stirred for 15 min, and a dichloromethane solution of the alcohol **95** (0.15 g, 0.5 mmol) was added dropwise at -60°C. The mixture was allowed to warm up to 0°C.

Triethylamine (2 mL) in dichloromethane (2 mL) was added dropwise and the reaction was warmed up to room temperature. It was then poured into 20 mL of ice-cold water and the organic layer separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ethyl acetate in hexane, gave pure aldehyde **96** (130 mg, 89% yield) as a colourless paste; ir ($CHCl_3$ cast): 1672 (C=O), 1147 and 1108 cm^{-1} (C-O-C); cims m/z: 298 ($M + NH_4^+$); hrms M^+: 280.2038 (calcd.for $C_{17}H_{28}O_3$: 280.2038); ^1H nmr ∂: 9.80 (d, 1H, J = 3 Hz, -CHO), 5.62 (bs, 1H, CH_3-C=C**H**-), 4.63 (d, 1H, J = 12 Hz, -O-C**H**H-O-), 4.60 (d, 1H, J = 12 Hz, -O-CH**H**-O-), 3.41 (d, 1H, J = 10 Hz, -C**H**H-OCH_2O-), 3.37 (s, 3H, -OCH_3), 3.25 (d, 1H, J = 10 Hz, -CH**H**-OCH_2O-), 2.84 (bs, 1H, C**H**-CHO), 1.98 (bs, 3H, =C-CH_3), 0.98 and 0.75 (each s, 3H each, *gem*-dimethyl). ^{13}C nmr ∂: 203.03, 126.42, 123.33, 95.67, 75.34, 57.66, 54.30, 40.55, 40.37, 38.09, 32.27, 31.50, 28.84, 23.22, 22.86, 21.73 and 18.52.

B. *Using Pyridinium Chlorochromate*

To a stirred slurry of pyridinium chlorochromate (70 mg, 0.3 mmol) in 5 mL of dichloromethane was added in one portion a solution of alcohol **95** (60 mg, 0.2 mmol) in 2 mL of dichloromethane at room temperature. The resulting dark brown solution was stirred at room temperature for 3 h and diluted with ether. The ethereal solution was filtered over magnesium sulfate. The filtrate was concentrated and the residue, on column chromatography, eluting with 5% ethylacetate, in hexane gave **96** (47 mg, 80% yield). The compound thus obtained was in all respects identical with the one obtained by Swern's oxidation procedure described above

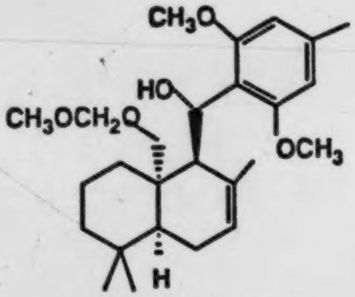
Orcinol Dimethyl Ether (98)



98

To a solution of orcinol (15.0 g, 0.12 mol) in 90 mL of methanol, sodium metal (6.0 g, 0.25 g-atom) was slowly added. The mixture was refluxed for 30 min. Dimethyl sulfate (ca. 50 mL) was slowly added until a light red solution was obtained. A 30% aqueous solution of sodium hydroxide was gradually added until a pale yellow solution was obtained. The addition of dimethyl sulfate and sodium hydroxide were alternated for three times. To the final alkaline solution, water was added and the resulting solution was extracted with ether. The ethereal extracts were washed with 30% aqueous sodium hydroxide, 10% acetic acid and water, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was distilled at 110°C and 117 mm pressure to give pure orcinol dimethyl ether **98** (16.5 g, 90% yield) as a colourless oil; ir (neat): 1607 and 1597 cm^{-1} (Ar-O-C); hrms M$^+$: 152.0841 (calcd. for $C_9H_{12}O_2$: 152.0837); ^{1}H nmr: ∂6.36 (s, 3H, aromatic), 3.76 (s, 6H, -OCH$_3$) and 2.20 (s, 3H, Ar-CH$_3$).

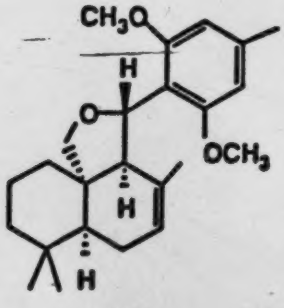
(1S,2S*,6S*)-10-(2,6-Dimethoxy-4-methyl-hydroxybenzyl)-1-methoxymethoxymethyl-3,7,7-trimethylbicyclo[4.4.0]dec-3- ene* ***(103)***



103

To a solution of orcinol dimethyl ether **98** (140 mg, 1 mmol) in 5 mL of ether under an argon atmosphere was added *n*-butyllithium (36 mg, 0.5 mmol). The resulting solution was stirred at room temperature for 2 h and then cooled to -78°C. Magnesium bromide etherate (146 mg, 0.5 mmol) was added in one portion and the resulting mixture stirred for 10 min. Aldehyde **96** (53 mg, 0.2 mmol) in 1 mL of ether was added slowly. The mixture was allowed to warm up to room temperature. After 2 h water was added. The organic layer was separated and washed with 1 N hydrochloric acid and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ethyl acetate in hexane, gave pure alcohol **103** (60 mg, 70% yield) as a white solid; ir (CHCl$_3$ cast): 3540 cm^{-1} (O-H); hrms m/z: 370.2506 (M$^+$ - 62, calcd. for C$_{24}$H$_{34}$O$_3$: 370.2507), and 181.0865 (base peak, calcd. for C$_{10}$H$_{13}$O$_3$: 181.0865); ^{13}C nmr ∂: 157.64, 137.86, 137.34, 126.29, 124.25, 118.32, 106.41, 104.33, 98.93, 96.79, 94.65, 68.97, 67.66, 67.01, 65.86, 63.96, 58.37, 56.46, 54.55, 52.44, 24.73, 16.09 and 14.42; ^{1}H nmr ∂: 6.36 (s, 2H, aromatic), 5.86 (m, 1H, CH$_3$-C=C**H**-), 5.44 (dd, 1H, J = 10, J' = 4 Hz, -C**H**-OH), 4.62 (d, 1H, J = 7 Hz, -O-C**H**H-O-), 4.38 (d, 1H, J = 7 Hz, -O-CH**H**-O-), 4.00 (d, 1H, J = 10 Hz, -C**H**-CHOH), 3.80 (s, 6H, 2 x Ar-OCH$_3$), 3.32 (s, 3H, -OCH$_3$), 3.22 (d, 1H, J = 10 Hz, -C**H**H-OCH$_2$O-), 2.98 (d, 1H, J = 10 Hz, -CH**H**-OCH$_2$O-), 2.24 (s, 3H, Ar-CH$_3$), 1.44 (s, 3H, =C-CH$_3$), 1.10 and 0.92 (each s, 3H each, *gem*-dimethyl).

(1S,4S*,5S*,9S*)-4-(2,6-Dimethoxy-4-methylphenyl)-3-oxa-6,10,10-trimethyltricyclo[7.4.0.0^{1,5}]tridec-6-ene* (**104**)



104

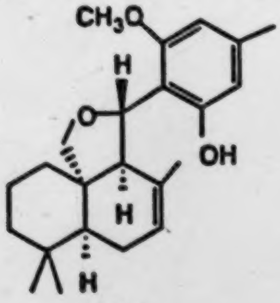
A. *Using Pyridine Hydrochloride*

A solution of alcohol **103** (110 mg, 2.5 mmol) and pyridine hydrochloride (58 mg, 5 mmol) in dichloromethane (10 mL) was refluxed under an argon atmosphere for 3 h. Water was added to the reaction mixture and the organic layer separated, washed with aqueous saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ethyl acetate in hexane, gave pure **104** (94 mg, 100% yield) as a white solid; m.p. 179-181°C (hexane), ir (CHCl$_3$ cast): 1608, 1560 (Ar-O-C), and 1125 cm^{-1} (C-O-C); hrms M$^+$: 370.2510 (Calcd. for $C_{24}H_{34}O_3$: 370.2508); ^{13}C nmr ∂: 140.44, 131.59, 121.09, 76.59, 75.89, 70.48, 55.80, 51.64, 47.26, 46.73, 33.94, 33.16, 29.71, 29.38, 27.96, 27.88, 22.04, 21.99, 19.81, 18.98 and 15.28; ^{1}H nmr ∂: 6.30 (s, 2H, aromatic), 5.34 (d, 1H, J = 12 Hz, Ar-CH-O-), 5.18 (bs, 1H, CH$_3$-C=CH-), 4.22 (d, 1H, J = 8 Hz, -CHH-O-CHAr), 3.78 (s, 6H, 2 x Ar-OCH$_3$), 3.66 (dd, 1H, J = 8, J' = 2 Hz, -CHH-O-CHAr), 2.34 (s, 3H, Ar-CH$_3$), 1.58 (t, 3H, J = 1 Hz, =C-CH$_3$), 0.96 and 0.84 (s each, 3H each, *gem*-dimethyl). Anal Calcd. for $C_{24}H_{34}O_3$: C,78.78; H, 9.25; Found C, 78.75; H, 8.97.

B. *Using Swern's Oxidation Procedure.*

To a solution of oxalyl chloride (20 mg, 0.16 mmol) and dimethyl sulfoxide (30 mg, 0.32 mmol) in 5 mL of dichloromethane at -60°C, was added alcohol **103** (35 mg, 0.08 mmol) in 2 mL of dry dichloromethane. The resulting solution was stirred under an argon atmosphere and gradually warmed to -10°C. Triethylamine (40 mg, 0.4 mmol) was added and the solution was warmed to room temperature. Ice-cold water was added and the resulting solution was extracted with dichloromethane. The extracts were washed with a saturated solution of aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with a 5% solution of ethyl acetate in hexane, gave pure **104** (15 mg, 51% yield).

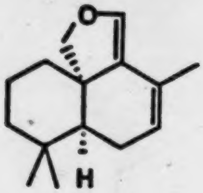
(1S,4S*,5S*,9S*)-4-(2[illegible]droxy-6-methoxy-4-methyl phenyl)-6,10,10-trimehyl-3-oxa[illegible]yclo[7.4.0.0^{1,5}]tridec-6-ene* **(105)**



105

To a solution of potassium hydride (35% dispersion in oil, 25 mg, 2.2 mmol), in 2 mL of *N,N*-dimethylformamide, was added ethanethiol (14 mg, 2.2 mmol). The mixture was stirred at room temperature under an argon for 5 min. A solution of cyclic ether **104** (17 g, 0.45 mmol) in 1 mL of *N,N*-dimethylformamide was added to it. After being heated for 12 h at 130°C, the reaction mixture was cooled to room temperature and a 6 N aqueous solution of hydrochloric acid was added dropwise until pH 1. The reaction mixture was then extracted with ether. The extracts were washed with aqueous saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with a 10% solution of ethyl acetate in hexane, gave pure **105** (11 mg, 67% yield); m.p. 149-151°C (hexane); ir ($CHCl_3$ cast): 3360 (O-H), 1585 (Ar-O-C) and 1101 cm^{-1} (C-O-C); hrms m/z: 355.2236 (M^+-1, calcd. for $C_{23}H_{31}O_3$: 355.2273); ^1H nmr ∂: 7.80 (s, 1H, -OH), 6.38 and 6.22 (each s, 1H each, aromatic), 5.40 (d, 1H, J = 10 Hz, Ar-CH-O-), 5.28 (bs, 3H, CH_3-C=C**H**-), 4.26 (d, 1H, J = 11 Hz, -C**H**H-O-), 3.74 (s, 3H, Ar-OCH_3), 3.68 (d, 1H, J = 11 Hz, -CH**H**-O-), 2.38 (s, 3H, Ar-CH_3), 1.56 (s, 3H, =C-CH_3), 0.92 and 0.84 (s each, 3H each, *gem*-dimethyl).

(1R,9S*)-6,10,10-Trimethyl-3-oxatricyclo[7.3.0.0^{1,5}]tridec-4,6-diene **(106)** and Orcinol Monomethyl Ether **(107)***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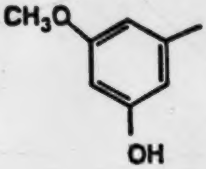
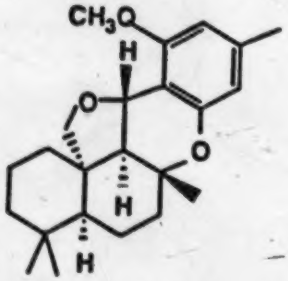

107

To a solution of phenol **105** (10 mg, 0.03 mmol) in 2 mL of dichloromethane at 0°C, was added boron trifluoride etherate (ca. 2 drops). The resulting pink solution was stirred under an argon atmosphere and was gradually warmed to room temperature. During this period, the colour of the solution was discharged. After 30 min water was added and the resulting mixture extracted with dichloromethane. The organic extracts were washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with a 10% solution of ethyl acetate in hexane, gave diene ether **106** (4 mg, 61% yield); ir ($CHCl_3$ cast): 1260 cm^{-1} (=C-O-C); hrms M$^+$: 218.1688 (Calcd. for $C_{15}H_{22}O_2$: 218.1671); ^{1}H nmr ∂: 6.26 (bs, 1H, -O-CH=C), 5.26 (bs, 1H, CH$_3$-C=C**H**-), 4.56 (d, 1H, J = 7 Hz, -C**H**H-O-), 3.80 (d, 1H, J = 7 Hz, -CH**H**-O-), 1.76 (bs, 3H, =C-CH$_3$), 0.86 and 0.82 (each s, 3H each, *gem*-dimethyl). Further elution with 15% ethyl acetate in hexane, gave orcinol monomethyl ether **107** (3 mg, 72% yield); ir ($CHCl_3$ cast): 3400 (OH), 1597 cm^{-1} (Ar-O-C); hrms M^+: 138.0680 (Calcd. for $C_8H_{10}O_2$: 138.0680); ^1H nmr ∂: 6.30, 6.24 and 6.20 (each s, 1H each, aromatic), 3.74 (s, 3H, $-OCH_3$) and 2.24 (s, 3H, $Ar-CH_3$).

Isosiccanin Methyl Ether (109)

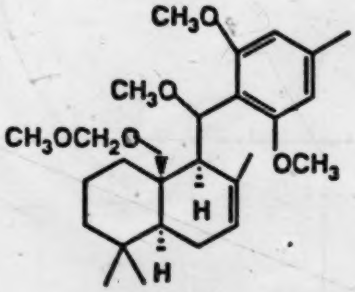


109

Phenol **105** (25 mg, 0.07 mmol) was dissolved in 2 mL of methanol. To this solution, mercuric acetate (110 g, 0.35 mmol) was added and the resulting solution was stirred under an argon atmosphere at room temperature for 8 h. Sodium borohydride (5 mg, 0.1 mmol) was added and the mixture was stirred for 30 min. The resulting solution was concentrated and the residue was extracted with ether. The ethereal extracts were washed with a saturated solution of aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with a 5% solution of ethyl acetate in hexane, gave pure isosiccanin methyl ether **(109)**

(18 mg, 72% yield) as a white solid; m.p. 208-209°C (hexane); ir ($CHCl_3$ cast): 1616 (Ar-O-C) and 1114 cm^{-1} (C-O-C); hrms m/z: 271.1332 (M^+ - 85, calcd. for $C_{17}H_{19}O_3$: 271.1334); ^1H nmr ∂: 6.32 and 6.24 (each s, 1H each, aromatic), 5.56 (bs, 1H, Ar-CH-O-), 4.16 (d, 1H, J = 8 Hz, -C**H**H-O-), 3.80 (s, 3H, -OCH_3), 3.56 (dd, 1H, J = 8, J' = 1 Hz, -CH**H**-O-), 2.28 (s, 3H, Ar-CH_3), 1.50 (s, 3H, -OC-CH_3), 0.84 and 0.82 (each s, 3H each, *gem*-dimethyl).

(1S,2S*,6S*)-2-(2,6-Dimethoxy-4-methyl-methoxybenzyl)-1-methoxymethoxymethyl-3,7,7-trimethyl bicyclo[4.4.0]dec-3-ene.* ***(114)***



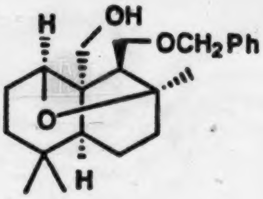
114

Potassium hydride (35% dispersion in oil, 30 mg, 0.2 mmol) was washed three times with freshly distilled 1,2-dimethoxyethane. It was then suspended in 5 mL of 1,2-dimethoxyethane and stirred at 0°C under an argon atmosphere. Alcohol **103** (20 mg, 0.48 mmol) in 2 mL of 1,2-dimethoxyethane was added dropwise to the suspension. After 5 min, methyl iodide (20 mg, 1.4 mmol) was added. The mixture was stirred for 3 h at room temperature, water was added and the mixture extracted with ether. The ethereal extracts were washed with 1 N aqueous hydrochloric acid and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ethyl acetate in hexane, gave pure **110** (18 mg, 83% yield); ir ($CHCl_3$ cast): 1608 (Ar-O-C), 1110 and 1097 cm^{-1} (C-O-C); hrms m/z: 370.2506. (M^+-76, calcd. for $C_{24}H_{34}O_3$ = 370.3508) and 195.0993 (base peak, calcd. for $C_{11}H_{15}O_3$ = 195.1111); ^1H nmr ∂: 6.36 (bs, 2H, aromatic), 5.72 (bs, 1H, CH_3-C=C$\mathbf{H}$-), 4.92 (d, 1H, J = 10 Hz, -O-CH-Ar), 4.64 (s, 2H, -O-CH_2-O-), 4.80 (s, 6H, 2 x Ar-OCH_3), 3.46 (d, 1H, J = 11 Hz, -C$\mathbf{H}$H-OCH_2O-), 3.36 (s, 3H, Ar-C-OCH_3), 3.10 (s, 3H, -CH_2-O-C$\mathbf{H}_3$), 3.08 (d, 1H, J= 11 Hz, -CH$\mathbf{H}$-OCH_2O-), 2.32 (s,3H, Ar-CH_3), 1.84 (t, 3H, J = 1 Hz, =C-CH_3), 1.04 and 0.88 (s each, 3H each, *gem*-dimethyl).

*Compound **105** from Ether **114**.*

Ether **114** (20 mg, 0.04 mmol) in 1 mL of *N,N*-dimethylformamide was added to a mixture of potassium hydride (35% dispersion in oil, 8 mg, 0.2 mmol) and ethanethiol (12 mg, 0.2 mmol) in 5 mL of *N,N*-dimethylformamide. The resulting solution was heated under an argon atmosphere at 125°C for 8 h and then cooled to room temperature. The solution was acidified (pH 1) with 6 N hydrochloric acid and extracted with ether. The extracts were washed with a saturated solution of aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with a solution of 15% ethyl acetate in hexane, gave pure phenol 105 (9 mg, 60% yield).

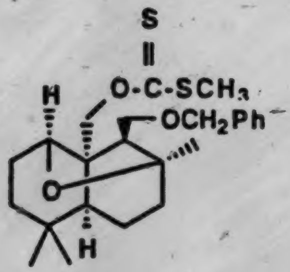
(1R,3R*,6S*,10S*)-10-Hydroxymethyl-3,3,7-trimethyl-2-oxa-tricyclo[4.3.1.1.^{3,10}]undecane* ***(122)***



122

A solution of diol **74** (330 mg, 0.9 mmol) and aqueous solution of 1 N hydrochloric acid (2 mL) in tetrahydrofuran (10 ml) was heated to reflux for 3 h under an argon atmosphere. The resulting solution was cooled to room temperature and extracted with ether. The ethereal extracts were washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with a 15% solution of ethyl acetate in hexane, gave pure hydroxy ether **122** (200 mg, 59% yield); ir (CH_2Cl_2 cast): 3510 (OH) and 1107 cm^{-1} (C-O-C); hrms M$^+$: 344.2353 (Calcd. for $C_{22}H_{32}O_3$: 344.2351); ^{1}H nmr ∂: 7.42 (m, 5H, aromatic), 4.62 (s, 2H, -OCH$_2$Ph), 3.25 (dd, 1H, J = 8, J' = 4 Hz, -OH), 1.25 (s, 3H, -OC-CH$_3$), 1.16 and 1.08 (each s, 3H each, *gem*-dimethyl).

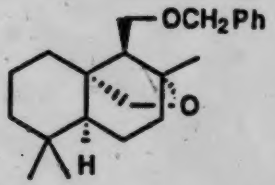
(1R,3R*,6S*,10S*)-10-Methylmercaptothionocarbonyloxy-3,3,7-trimethyl-2-oxa-tricyclo[4.3.1.1.^{3,10}]undecane* **(123)**



123

Sodium hydride (50% dispersion in oil, 70 mg, 2.8 mmol) was washed 3 times with freshly distilled 1,2-dimethoxyethane. It was then suspended in 10 mL of 1,2-dimethoxyethane under an argon atmosphere and cooled to 0°C. A solution of alcohol **122** (200 mg, 0.55 mmol) in 5 mL of 1,2-dimethoxyethane was slowly added to the suspension. After stirring for 10 min, carbon disulfide (1 mL) and methyl iodide (1 mL) were added. The reaction mixture was stirred at room temperature for 6 h, and then cooled to 0°C. Water was added slowly to the reaction mixture and the resulting solution was extracted with dichloromethane. The organic layer was washed with aqueous 1 N hydrochloric acid and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ethyl acetate in hexane, gave pure **123** (140 mg, 58% yield) as a pale yellow oil; ir ($CHCl_3$ cast): 1240 cm^{-1} (C=S); hrms M^+: 434.1947 (calcd. for $C_{24}H_{34}S_2O$: 434.1950); ^1H nmr ∂: 7.30 (s, 5H, aromatic), 4.83 (d, 1H, J = 12 Hz, -C**H**H-OCS), 4.56 (d, 1H, J = 12 Hz, -CH**H**-OCS), 3.90 (bs, 1H, -C**H**HOCH$_2$Ph), 3.58 (dd, J = 6, J' = 2 Hz, -CH**H**OCH$_2$Ph), 2.52 (s, 3H, -SCH$_3$), 1.30 (s, 3H, -OC-CH$_3$), 1.02 and 0.98 (each s, 3H each, *gem*-dimethyl).

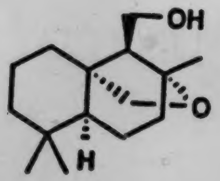
(1R,4R*,7S*,12S*)-12-Benzyloxymethyl-4,8,8-trimethyl-3-oxatricyclo[4.3.1.1.^{1,4}]dodecane (120)*



120

A solution of alcohol **91** (340 mg, 1.2 mmol) and aqueous solution of 1 N hydrochloric acid (2 mL) in tetrahydrofuran (10 mL) was heated to reflux for 3 h under an argon atmosphere. The resulting solution was cooled to room temperature and extracted with ether. The ethereal extracts were washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with a 5% solution of ethyl acetate in hexane, gave pure hydroxy ether **120** (150 mg, 53% yield); ir (neat): 1073 cm^{-1} (C-O-C); hrms M$^+$: 328.2399 (calcd. for $C_{22}H_{32}O_2$: 328.2402); ^{1}H nmr ∂: 7.40 (s, 5H aromatic), 4.64 (d, 1H, J = 12 Hz, -OC**H**HPh), 4.52 (d, 1H, J = 12 Hz, -OCH**H**Ph), 3.96 (dd, 1H, J = 8, J' = 5 Hz, -C**H**H-OCH$_2$Ph), 3.62 (t, 1H, J = 8 Hz, -CH**H**-OCH$_2$Ph), 1.52 (s, 3H, -OC-CH$_3$), 0.96 and 0.84 (each s, 3H each, *gem*-dimethyl).

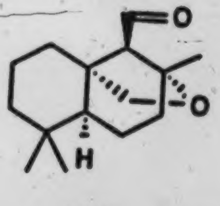
(1R,4R*,7S*,12S*)-12-hydroxymethyl-4,8,8-trimethyl-3-oxatricyclo[4.3.1.1.^{1,4}]dodecane* ***(124)***



124

At -78°C, a solution of benzyl ether **120** (450 mg, 1.4 mmol) in 10 mL of ether and *t*-butyl alcohol (ca. 5 drops) was added, over a period of 5 min, to freshly distilled ammonia (15 mL) under an argon atmosphere. Lithium metal (100 mg, 0.014 g-atom) was added in small portions. The resulting blue coloured solution was stirred for 3 h, during which period the blue colour was discharged. Methanol was added dropwise and the excess of ammonia was allowed to evaporate at room temperature overnight. Water was added and the resulting solution was extracted with ether. The ethereal extracts were washed with 1N aqueous hydrochloric acid and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 25% ethyl acetate in Hexane, gave pure alcohol **124** (270 mg, 83% yield); ir ($CHCl_3$ cast): 3420 cm^{-1} (OH); hrms M^+: 238.1938 (calcd. for $C_{15}H_{26}O_2$: 238.1933); ^1H nmr ∂: 3.70- 3.40 (m, 4H, $-CH_2O-$ and $-CH_2OH$), 1.30 (s, 3H, $-OC-C\underline{H}_3$), 0.90 and 0.80 (each s, 3H each, *gem*-dimethyl.

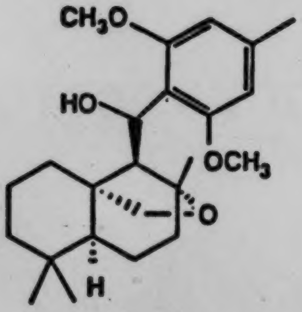
(1R,4R*,7S*,12S*)-12-Formyl-4,8,8-trimethyl-3-oxa-tricyclo[4.3.1.1.^{1,4}]dodecane* ***(125)***



125

To a slurry of pyridinium chlorochromate (110 mg, 0.5 mmol) in 10 mL of dichloromethane, was added a solution of alcohol **119** (40 mg, 0.17 mmol) at room temperature. The mixture was stirred under an argon atmosphere for 4 h. It was then diluted with ether, filtered through magnesium sulfate and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ethyl acetate in hexane, gave pure aldehyde **125** (22 mg, 81% yield); ir ($CHCl_3$ cast): 1740 cm^{-1} (C=O); hrms M^+: 236.1782 (calcd. for $C_{15}H_{24}O_2$: 236.1788); ^1H nmr ∂: 10.6 (d, 1H, J = 2 Hz, -CHO), 3.70 (s, 2H, $-OCH_2-$), 1.58 (s, 3H, $-OC-CH_3$), 0.92 and 0.80 (each s, 3H each, *gem*-dimethyl).

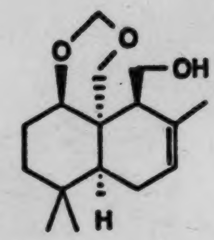
(1R,4R*,7S*,12S*)-12-(2,6-Dimethoxy-4-methyl-hydroxybenzyl)-4,8,8-trimethyl-3-oxa-tricyclo[4.3.1.1.^{1,4}]dodecane* ***(126)***



126

At 0°C,to a solution of orcinol dimethyl ether (130 mg, 0.85 mmol) in 5 mL of ether under an argon was added n-butyl lithium (33 mg, 0.51 mmol) in hexane. After stirring for 2 h aldehyde **125** (40 mg, 0.17 mmol) in 2 mL of ether was slowly added. The mixture was allowed to warm up to room temperature. After 2 h, water was added. The mixture was extracted with ether. The extracts were washed with aqueous 1 N hydrochloric acid and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with a 15% solution of ethyl acetate in hexane, gave orcinol dimethyl ether (0.03 g). Further elution gave alcohol **126** (60 mg, 91% yield); ir ($CHCl_3$ cast): 3400 (OH) and 1120 cm^{-1} (C-O-C); hrms m/z: 370.2506 (M^+ - 18, calcd. for $C_{24}H_{34}O_3$: 370.2510); ^1H nmr ∂: 6.46 (s, 2H, aromatic), 5.62 (dd, 1H, J = 8, J' = 2 Hz, -C**H**OH), 3.82 (s, 6H, $-OCH_3$), 3.50 (d, 1H, J = 11 Hz, -C**H**H-O-), 3.24 (d, 1H, J = 11 Hz, -CH**H**-O-), 2.32 (s, 3H, $Ar-CH_3$), 1.70 (s, 3H, $-OC-CH_3$), 1.16 and 0.92 (each s, 3H each, *gem*-dimethyl).

(1R,6R*,10S*,14S*)-14-Hydroxymethyl-3,5-dioxa-9,9,13-trimethyltricyclo[8.4.0.0^{1,6}]tetradec-12-ene.* **(127)**

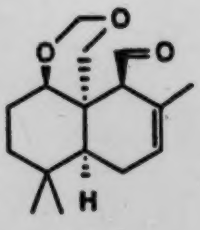


127

At -78°C, a solution of benzyl ether **83** (1.50 g, 4.0 mmol) in ether (10 mL) and t-butylalcohol (ca. 1ml) was added over a period of 5 min to freshly distilled ammonia (25 mL) under argon atmosphere. Lithium metal (400 g, 0.056 g-atom) was added in small portions over a period of 5 min. The resulting blue coloured solution was stirred for 5 h, during which period the blue colour was discharged. Methanol was added dropwise and the excess of ammonia was allowed to evaporate at room temperature overnight. Water was added and the resulting solution was extracted with ether. The ethereal extracts were washed with aqueous 1 N hydrochloric acid solution and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 25% ethyl acetate in hexane, gave pure **127** (618 mg, 55% yield); ir ($CHCl_3$ cast): 3540 (O-H), 1174 and 1106 cm^{-1} (C-O-C); hrms m/z: 248.1788 (M^+-18, calcd. for $C_{16}H_{24}O_2$: 248.1786); ^1H nmr ∂: 5.40 (bs, 1H, CH_3-C=CH-), 5.21 (d, 1H, J = 8 Hz, -O-

CHH-O-), 4.86 (d, 1H, J = 8 Hz, -O-CHH-O-), 3.98 (m, 1H, -OCH_2O-CH-), 3.80 (d, 1H, J = 11 Hz, -CHH-OCH_2O-), 3.18 (d, 1H, J = 11 Hz, -CHH-OCH_2O-),1.80 (s, 3H, =C-CH_3), 0.96 and 0.82 (each s, 3H each, *gem*-di-methyl).

(1R,6R*,10S*,14S*)-14-Formyl-3,5-dioxa-9,9,13- trimethyl tricyclo[8.4.0.0 ^{1,6}]tetradec-12-ene **(128)***

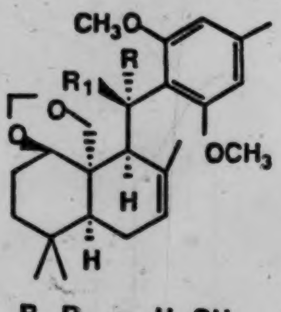


128

To a slurry of pyridinium chlorochromate (300 mg, 1.4 mmol) in 10 mL of dichloromethane, was added a solution of alcohol **127** (250 mg, 0.9 mmol) in 2 mL of dichloromethane at room temperature. The mixture was stirred under an argon atmosphere for 4 h. It was then diluted with ether, filtered through magnesium sulfate and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ethyl acetate in hexane, gave pure aldehyde **128** (198 mg, 80% yield) as a viscous oil; ir ($CHCl_3$ cast): 2858 (CHO), 1711 (C=O), 1175 and 1105 cm^{-1} (C-O-C); hrms M^+: 264.1720 (Calcd. for $C_{16}H_{24}O_3$: 264.1726); ^1H nmr ∂: 10.16 (d, 1H, J = 2 Hz, -CHO), 5.70 (bs, 1H, CH_3-C=CH-), 5.26 (d, 1H, J = 9 Hz, -O-

CHH-O-), 4.82 (d, 1H, J = 9 Hz, -O-CHH-O-), 3.82 (d, 1H, J = 10 Hz, -CHH-OCH$_2$O-), 3.50 (m, 1H, -CH-OCH$_2$O-), 3.32 (d, 1H, J = 10 Hz, -CHH-OCH$_2$O-), 1.72 (bs, 3H, =C-CH$_3$), 0.90 and 0.68 (each s, 3H each, *gem*-dimethyl).

(1R,6R*,10S*,14S*)-14-(2,6-Dimethoxy-4-methyl-hydroxybenzyl)-9,9,13-trimethyl-3,5-dioxatricyclo[8.4.0.0^{1,6}]tetradec-12-ene* ***(129)***



R, R$_1$ = H, OH

129

To a solution of orcinol dimethyl ether (408 mg, 2.6 mmol) in 5 mL of ether under an argon atmosphere was added *n*-butyllithium (0.10 g, 1.5 mmol) in hexane. The resulting mixture was stirred at room temperature for 2 h and then cooled to -78°C. Magnesium bromide etherate (380 mg, 1.5 mmol) was added in one portion and the resulting mixture was stirred for 30 min. Aldehyde **128** (140 mg, 0.5 mmol) in 2 mL of ether was slowly added. The mixture was allowed to warm up to room temperature. After 2 h water was added. The resulting solution was extracted with ether. The extracts were washed with aqueous 1 N hydrochloric acid, saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 10% ethyl acetate in hexane, gave the major epimer of **129** (121 mg, 58% yield); ir ($CHCl_3$ cast): 3540 (O-H), 1607,1597 (Ar-O-C), 1172 and 1150 cm^{-1} (C-O-C); hrms m/z: 264.1730 (M$^+$-152, calcd. for $C_{16}H_{24}O_3$: 264.1725); ^{1}H nmr ∂: 6.30 (s, 2H, aromatic), 5.50 (bs, 1H, CH$_3$-C=C**H**-), 5.32 (d, 1H, J = 7 Hz, -O-C**H**H-O-), 4.82 (d, 1H, J = 7 Hz, -O-CH**H**-O-), 4.58 (bs, 1H, -C**H**OH), 3.78 (s, 6H, 2 x Ar-OCH$_3$), 3.68 (d, 1H, J = 10 Hz, -C**H**H-OCH$_2$O-), 3.44 (dd, 1H, J = 10, J' = 4 Hz, -C**H**H-OCH$_2$O-), 3.18 (d, 1H, J = 10 Hz, -CH**H**-OCH$_2$O-), 2.30 (s, 3H, Ar-CH$_3$), 1.80 (s, 3H, =C-CH$_3$), 0.98 and 0.92 (each s, 3H each, gem-di-methyl). Further elution with 15% ethyl acetate in hexane gave 35 mg (28% yield) of the minor epimer of **129**; ir ($CHCl_3$ cast): 3500 (O-H), 1610, 1582 (Ar-O-C), 1146 and 1124 cm^{-1} (C-O-C); hrms m/z: 398.2467 (M$^+$-18, calcd. for $C_{25}H_{34}O_4$: 398.2456); ^{1}H nmr ∂: 6.34 (s, 2H, aromatic), 5.82 (dd, 1H, J = 10, J' = 2 Hz, -C**H**OH), 5.64 (bs, 1H, CH$_3$-C=C**H**-), 5.18 (d, 1H, J = 7 Hz, -O-C**H**H-O-), 4.92 (d, 1H, J = 7 Hz, -O-CH**H**-O-), 4.30 (dd, 1H, J = 10, J' = 4 Hz, -C**H**-OCH$_2$O-), 3.76 (s, 6H, 2 x Ar-OCH$_3$), 3.52 (d, 1H, J = 10 Hz, -C**H**H-OCH$_2$O-), 3.10 (d, 1H, J = 10 Hz, -CH**H**-OCH$_2$O-), 2.30 (s, 3H, Ar-CH$_3$), 1.30 (bs, 3H, =C-CH$_3$), 1.18 and 0.92 (each s, 3H each, *gem*-dimethyl).

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